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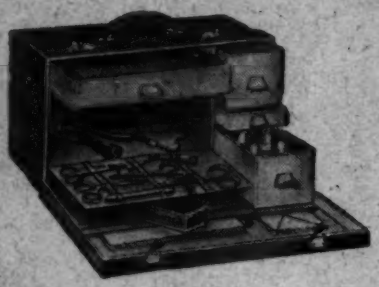

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BRITISH MEDICAL JOURNAL

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ACTION OF THE OVARIAN HORMONES ON UTERINE MUSCLE*

BY

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In 1907 Sir Henry Dale reported from his laboratory at Herne Hill the curious discovery that the uterus of the cat does not always react in the same way when its muscular tissue is stimulated through the hypogastric nerves or by intravenous injection of adrenaline. If the cat is not pregnant these stimuli cause relaxation of the uterus, but if she is pregnant they cause contraction. Before Dale's paper was printed Professor A. R. Cushny (1907) made identically the same observation at University College and reported it to the Physiological Society. Although it probably did not occur to either of these eminent pharmacologists that the reversal of muscular response which they had noticed was caused by action of the ovary, and although in fact "pregnancy reversal" still awaits detailed explanation, it was this observation that opened the way to study of the relation between the ovary and the behaviour of the uterine muscle.

In that same year the Heidelberg gynaecologist Erwin Kehrer (1907) was making his pioneer studies of uterine muscle *in vitro*, in which he applied the then very recent discovery of Rudolf Magnus that strips of involuntary muscle cut from the intestine will long remain active if immersed in warm oxygenated physiological salt solution. By attaching such a strip to a lever, the spontaneous isotonic contractions of the muscle and its response to stimulation can be registered. This beautifully simple method began at once to be used in every pharmacological laboratory where oxytocic drugs were studied, Kehrer himself leading the way. In 1908, reporting his first studies on the action of ergot derivatives, he recommended the use of young virgin cats, for he had found that uterine tissue from adult animals taken during the breeding season was often less active and less predictable in its responses. This precautionary specification of the virgin uterus for tests of oxytocic drugs was written into all the pharmacopoeias of the world long before it could be understood in the light of endocrinology.

In 1913 Max Stickel noticed that the movements of the rabbit's uterus *in situ* are greatly reduced by ablation of the ovaries, and a few years later (1919) Athias, of Lisbon, confirmed this fundamental observation by *in vitro* experiments on guinea-pigs' uteri by the Magnus–Kehrer method. Castration, he wrote, causes a gradual weakening of the automatic contractions to the point of disappearance. If, however, ovarian tissue is regrafted into the animal at the time of castration the uterus retains full power to contract spontaneously *in vitro*. Evidently uterine contractility depends upon an internal secretion of the ovaries. We shall be able, later in this lecture, to explain this remarkable fact, in part at least, on biochemical grounds. Thus, before the two ovarian hormones were isolated or even clearly foreshadowed, characteristic differences in the behaviour of uterine muscle were observed which we can now see were related to the action of progesterone and oestrogen respectively.

*Fourth Annual Ciba Foundation Lecture, delivered in London on December 4, 1952.

Shrewd Conjecture

One of us (G. W. C.) was fortunate in having in his laboratory, about the years 1921–2, a group of medical students doing research on various aspects of the ovarian cycle. Two of these young men, the twin brothers Guttmacher, happened to read Dale's paper of 1907, and made the suggestion that the changes in uterine response to adrenaline observed during pregnancy may be due to the action of the corpus luteum, and hence might be expected to occur also in non-pregnant animals during the corpus luteum phase of the reproductive cycle. This was an extraordinarily shrewd conjecture to be made by medical students. Going on to other studies, the Guttmachers were unable to test their conjecture, and with their consent it was turned over to another student. John D. Keye.

Keye was taught to utilize for this purpose the uteri of swine, which were readily available at an abattoir near the Johns Hopkins Medical School. The sow has a clearly defined reproductive cycle consisting of a follicular phase lasting one week, which culminates in oestrus and ovulation, during which oestrogen is the dominant hormone, and a corpus luteum phase about two weeks in length, during which progesterone is dominant. Such a sequence of events occurs, with various modifications, in all mammals that have been studied. In the rabbit, which is the chief subject of our contribution, oestrus is not periodic and ovulation does not occur spontaneously. Mature does will accept mating at almost any time, and then only do the follicles mature and rupture. The

follicular phase of the cycle (if we may speak of a cycle in this case) is therefore of indefinite length. The corpus luteum phase is ordinarily associated only with pregnancy, but an infertile mating (which may be arranged by the experimenter) gives rise to a corpus luteum phase or "pseudo-pregnancy" comparable in all respects to the corpus luteum phase of the sow's or the human cycle.

Uterine Contraction Pattern

For the purpose of Keye's investigation, strips from sows' uteri at various stages of the cycle were suspended in warm oxygenated salt solution by the Magnus–Kehrer technique, and were to be treated with adrenaline and other oxytocics. But Keye (1923) never arrived at that stage of the experiment, for we were amazed to find that the pattern of spontaneous contraction of the muscle, before treatment with oxytocic drugs, varies in a dramatic way throughout the cycle. At oestrus, when ripe follicles are present in the ovaries, the contractions are large and infrequent, occurring once every one or two minutes; during the corpus luteum phase they are small but very frequent, at the rate of five to eight a minute. By observing these changes and the transitions between them it was possible to characterize the contraction pattern almost from day to day of the cycle. Simultaneously with Keye's study, a student of H. M. Evans —Blair (1923)—found something of the same sort in rats, but the shortness of the cycle in that species obscures the pattern of uterine contraction and no further work was done on the rat.

When the ovarian hormones became available they were promptly put to use in following up the earlier observations on uterine contractility. In 1929 Van Dyke and Gustavson reproduced the Dale–Cushny "pregnancy reversal" in kittens treated with crude lipoidal corpus luteum extracts. In the same year S. R. M. Reynolds introduced his ingenious method of recording uterine contractility *in situ* by a small balloon inserted into the rabbit's uterus through a vaginal fistula. He showed (Reynolds, 1931) that spontaneous contractility is almost abolished by castration but is quickly restored by subcutaneous injections of oestrogenic hormone.

Interest in the relation between the hormones and uterine motility was now greatly stimulated by a series of contributions from Herman Knaus (1930). This investigator noticed that uteri of pregnant and pseudo-pregnant rabbits studied *in vitro* do not respond to "pituitrin" by vigorous contraction as do the uteri of virgin rabbits. Learning, as had Van Dyke and Gustavson, of the corpus luteum hormone recently isolated by Corner and W. M. Allen, Knaus made the first crude progesterone produced in Europe, and with it induced in the virgin uterus an altered response to pituitrin resembling that seen in his earlier experiments on pregnant and pseudo-pregnant rabbits. As soon as crystalline progesterone was available, Makepeace, Corner, and Allen (1936) obtained the same result with the pure hormone. Reynolds and Allen (1932) found also that the large, regular, relatively infrequent contractions observed by the Reynolds fistula technique in oestrous rabbits or after oestrogen treatment are almost totally suppressed for hours by a single subcutaneous injection of progesterone. J. M. Robson (1936) added much to our detailed knowledge of the action of oxytocic hormones under varying hormonal conditions.

Beyond this point there has been no significant progress. Summarizing what has been learned, we see that (1) oestrogen is necessary for spontaneous motility; (2) the pattern of spontaneous contraction differs greatly according to the dominant hormone—namely, oestrogen in the unmated and oestrous rabbit, progesterone in pregnancy and in the corpus luteum phase of the cycle (pseudo-pregnancy); (3) the response to stimulation by certain oxytocic drugs may also differ under different hormone domination.

The observed facts cannot all be fitted together, nor do they permit, as yet, effective theorizing about their functional significance for the behaviour of the uterus as a whole organ. They do, however, provide the basis for a new effort to discover, at the level of the muscle cell, and in biochemical terms, the mechanisms by which the ovarian hormones actually control uterine motility.

Molecular Physiology

For a clearer insight into the myometrial cell we must turn to molecular physiology. One single contraction–relaxation cycle of the uterus, observed in the obstetrical ward as a labour pain, or registered *in vivo* or *in vitro* by the techniques of classical physiology, is clearly a complex phenomenon involving a whole series of elementary events. In 1946 one of us (A. C.), a clinical obstetrician at the time, became convinced, after reading the articles of Szent-Györgyi and his associates, that the function of the myometrium, like that of the voluntary muscle which they were studying, could be understood only if the complexity of the contractile system were broken into simpler component elements and analysed step by step with biochemical and physico-chemical techniques. It was to be hoped that the system thus taken apart can gradually be put together again.

Muscle contraction involves basically a contractile substance, a supply of energy, a stimulus to initiate the contraction, and a means of conducting the stimulus to the contractile elements. Study of the process must be directed toward these four basic systems. The research which we here summarize began with the final contractile substance because, thanks to the efforts of the biochemists, it was far better characterized than any of the other systems.

Szent-Györgyi (1945) greatly simplified the problem by showing that "contraction" can be produced *in vitro* by merely bringing together the isolated constituents of the process—namely, the fibrous protein complex actomyosin (A.M.), the energy-rich nucleotide adenosine triphosphate (A.T.P.), and ions. Thus he claimed that muscle contraction in a final sense is an interreaction between A.M., A.T.P., and ions. His observation was the climax of a long extensive study conducted in several laboratories of different countries and led by outstanding biochemists and physical chemists (see for literature Szent-Györgyi, 1951).

Actomyosin

It is now a textbook statement that the final contractile substance of skeletal muscle is A.M. This complex, first recognized by Banga and Szent-Györgyi (see Szent-Györgyi, 1945), was decomposed in the latter's laboratory into its two component proteins, myosin (M.) and actin (A.). Actin-free myosin was prepared in pure ("crystalline") form by Szent-Györgyi himself, and actin was purified by his pupil Straub. A.T.P., the compound containing high-energy phosphate bonds (~ph) was first demonstrated in muscle by Lohmann (1938). Myosin, as Engelhardt and Ljubimowa (1939) have shown, has the property of acting as an enzyme (more specifically, as an adenosine triphosphatase) which can break the high-energy linkage of the terminal phosphate of A.T.P. and release its free energy, calculated by Meyerhof to be 11,000 calories.

Weber (1935), who extracted from muscle a "myosin gel" (now known to consist of actomyosin), was able to form it into fibres similar in appearance to fine cotton threads. Szent-Györgyi (1945) showed that such threads of A.M. will shorten when A.T.P. is added if they are suspended in a salt solution similar in ionic strength to serum. Objections were raised in various laboratories against the idea of analogy between this thread-contraction phenomenon and muscle contraction. This criticism led to the effort to make the molecular structure of the A.M. thread more like the structure of muscle. This was done by stretching the A.M. fibres, so that the A.M. micelles become parallel as they are in muscle. Such threads shorten and become thicker without changing volume. This effort culminated in Szent-Györgyi's preparation of glycerin-treated psoas muscle from the rabbit (Szent-Györgyi, 1947,

1951) in which the muscle-cell membrane is destroyed (in a functional sense as indicated by the loss of electrical excitability) and the water-soluble components are removed, but the contractile proteins preserve their architecture. When A.T.P. is added, such fibres develop tension similar to that of intact muscle. Taking all the opinions into account, Mommaerts (1950) wrote in his recent survey: "It seems justified to conclude that Szent-Györgyi actually succeeded in a dissolution, separation, and resynthesis of the contractile system."

With the information thus briefly outlined in hand, let us turn to the uterus and ask whether the final contractile system in the myometrium is fundamentally the same as that of skeletal muscle. With modifications required by the smaller amount of material available and the difference in structure, Csapo (1948, 1950a) succeeded in isolating A.M. from human, rabbit, rat, and cow uteri.

All tests performed so far on the A.M. of the uterus support the conclusion that it is fundamentally the same as that of skeletal muscle. It is true that slight differences have been observed between the two substances, which may be partly responsible for the differences between the two kinds of muscle long known to physiologists. First, however, let us consider the similarities.

Characteristics of Actomyosin

What are the characteristics of actomyosin? (see literature, Szent-Györgyi, 1951). A.M. can be extracted from fresh muscle by 0.5 mol KCl, and can be purified simply by precipitation by dilution. If redissolved in 0.5 mol KCl it has a high anomalous viscosity, which indicates that it is made up of highly asymmetric particles. If the purified extract is studied in the Svedberg ultracentrifuge or the Tiselius electrophoretic apparatus it tends to be distributed into two portions, yielding curves with a larger peak which represent A.M. and a smaller peak representing free M. uncombined with A. (Snellman and Erdös, 1984a, 1948b).

If A.T.P. is added to A.M. in the viscosimeter an immediate drop in viscosity will be observed. The viscosity of the component proteins, A. and M., being less than that of the complex, A.M., this drop in viscosity indicates the dissociation of the complex into its component parts. M. being an A.T.P.-ase, A.T.P. will be split and its dissociating effect on A.M. will be terminated; the A. and M. will then reassociate, combining to form A.M., as indicated by the gradual rise in viscosity. Actomyosin threads can be prepared from uterine muscle and will contract energetically when A.T.P. is added.

All the properties just mentioned are characteristic of uterine A.M. as well as that from skeletal muscle. As for the differences, observations by viscosimetry show that the amount of A.M. is much less in the uterus than in skeletal muscle (about one-seventh) and, moreover, A.M. forms only about one-third of the total amount of the contractile proteins, whereas in skeletal muscle extracts two-thirds is A.M. (Csapo, 1948, 1949, 1950a, 1950b).

By following the change of viscosity when A.T.P. is added to identical amounts of the two kinds of contractile proteins it is found (Csapo, 1949) that the recombination of uterine A.M. indicated by increase in viscosity does not begin as soon and does not proceed as fast as does that of skeletal muscle. This can be explained either by a lower A.T.P.-ase activity of the uterine extract or else by the lower activity of the myokinase system resulting in the accumulation of A.T.P. which keeps A.M. dissociated.

When the "contraction" of threads of the two kinds of actomyosin is compared (Csapo, 1950a), it is found that uterine A.M. contracts much more slowly than that from skeletal muscle, and with a longer "latent period" after the addition of A.T.P. Moreover, uterine A.M. threads contract only below the A.T.P. concentration of 4×10^{-3} mol. At this critical concentration the threads first lengthen before they contract, whereas above this concentration they completely dissolve. In contrast threads of similar A.M. concentration (obtained by dilution) from skeletal muscle readily contract even in a twenty-times higher concentration of A.T.P. solution (Csapo, unpublished).

Uterine A.M., unlike that of skeletal muscle, practically loses its ability to contract (Csapo, 1949) if precipitated only once (by dilution). This process is reversible, however, and the precipitated A.M. can be reactivated if fresh watery extract is added to the precipitate or to the salt solution in which the thread is suspended. The speed of thread contraction thus depends on a factor (or factors) present in the watery extract of the uterus, and the speed of contraction is directly related to the concentration of this factor, which we will call "X." Skeletal muscle also contains X-factor in a much higher concentration or else in a more active form (Csapo, 1949). This matter of the X-factor is mentioned to emphasize the possibility that the differences between skeletal and uterine muscle extracts are not all necessarily due to differences of the A.M. itself, but may well be due to differences in their prosthetic groups or other active substances attached to the A.M. framework. When highly purified actin and myosin from the uterus become available this question can be further studied.

In summary, the final contractile substance in uterine muscle is actomyosin, generally resembling the characteristics of the contractile protein-complex of skeletal muscle, but present in much lower concentration and forming a smaller fraction of the total proteins.

Effect of Ovarian Hormones on Contractile Proteins of Myometrium

Next let us examine the effect of the ovarian hormones upon the contractile proteins of the myometrium. In skeletal muscle the concentration of A.M. and the ratio of A.M. to free M. are found to be constant. In uterine muscle, however, the concentration of A.M. is significantly different under varying hormonal conditions of the ovaries. When a rabbit is castrated the concentration of A.M. drops to about one-fifth that found in the oestrous animal. In late pregnancy, on the other hand, the concentration is about twice as much as in oestrus. In oestrus, moreover, two-thirds of the contractile protein is free M. and only one-third is A.M., whereas in late pregnancy the ratio is reversed, as viscosimetry has shown. The same holds for the human as demonstrated by ultracentrifugation and electrophoresis. These observations already suggest that the concentration of uterine A.M. is under the control of the ovaries (Csapo, 1948, 1950a, 1950b; Csapo, Erdös, Naeslund, and Snellman, 1950).

Studying the course of the change in A.M. concentration during pregnancy in rabbits, we observed a slight drop in the first third, followed by a sharp increase in the second third. A high plateau is maintained in the last third of pregnancy with a climax at labour, after which the concentration of A.M. drops rapidly to the non-pregnant (oestrous) level. This curve gives a further indication that oestrogen is responsible for the changes in A.M. concentration of the uterus (Csapo, unpublished). Final evidence for this conclusion was given by the following experiments.

Rabbits were bilaterally ovariectomized and a few weeks later the previously mentioned great decrease in A.M. concentration of the uterus was observed as a result of the castration. Oestrogen was then administered, and a gradual increase in the A.M. concentration caused by the removal of both ovaries can be experimentally reversed by supplying oestrogen to the animal (Csapo, 1950b).

In another set of experiments it was found that progesterone does not have any such effect as oestrogen upon concentration of A.M. in the uterus (Csapo and Corner, 1951). We believe that the slight drop of A.M. concentration during the first week of rabbit pregnancy mentioned above is due to the decrease or disappearance of tissue oestrogen and not to the increasing action of progesterone.

How oestrogen controls A.M. concentration in the uterus we do not know as yet. As pointed out by D. Needham (1952), it is possible that oestrogen affects the formation of A.M. by providing a means by which the "building stones" or precursors (of smaller molecular weight) are bound together to form longer fibrous units. This mechanism cannot, however, be the only one involved in A.M. formation, since in an oestrogen-treated castrate rabbit the uterine weight increases ten to twenty times while the protein concentration per unit of weight is also increasing. Thus large amounts of proteins must be synthesized as a result of the action of oestrogen upon the uterus. It is worth emphasizing that in the uterus we possess a tissue in which the effect of oestrogen on protein synthesis has been experimentally established. In skeletal muscle similar changes have been observed only during embryonic and post-natal development (Csapo and Herrmann, 1951); once sexual maturation is complete the contractile proteins of skeletal muscle are not subject to hormonal control.

The concentration of A.M. in uterine muscle is, however, not alone affected by oestrogen; the properties of extracted A.M. are also changed. With the viscosimeter we find that the "splitting-time" of A.T.P. is reduced by oestrogen treatment and the recombination of dissociated A.M. after A.T.P. has been split becomes faster (Csapo, 1949). The speed of A.M. thread contraction is also increased, as shown in specimens from late pregnancy (Csapo, 1948, 1950a). We assume tentatively that the concentration or activity of the X-factor is also affected by oestrogen.

Relation of Ovarian Hormones to the Energy-yielding System of the Uterus

With this we conclude our brief summary of the facts known at present about uterine A.M. and its dependence upon oestrogen. The next inquiry concerns the relation of the ovarian hormones to the energy-yielding system of the uterus. Before proceeding any further we must recall Szent-Györgyi's thread-contraction experiments, from which it is evident that not A.M. but A.M.–A.T.P. is the final contractile substance. Experiments in our laboratory have shown (Csapo and Gergely, 1950) that the total high-energy phosphate content of the uterus is only about one-seventh that of skeletal muscle, and recent measurements by means of Kalckar's differential spectrophotometric technique show that the same ratio holds for A.T.P. in particular (Menkes and Csapo, unpublished). Others have observed similar or lower values for the ~ph content of the uterus (see for literature Walaas and Walaas, 1950a). Since the concentration of actomyosin in uterine muscle was also found to be one-seventh that of the skeletal muscle a stoicheiometric relationship may be assumed to exist between A.M. and A.T.P. The amount of A.T.P. present is much greater than is used in one concentration cycle, and since resynthesis of A.T.P. goes on with great speed the surplus may serve other purposes, such as to make the system complete and reactive. We calculated the amount of A.T.P. used in one contraction cycle and arrived at the figure of 0.25 micromols ~ph bond energy per gramme uterus per contraction (Csapo and Gergely, 1950). This value is identical with that calculated by A. V. Hill for skeletal muscle.

When the uterus is not under the influence of oestrogen its high-energy phosphate store is at a low ebb. In immature rabbits and also in adults after castration we found (Menkes and Csapo, 1952) a low concentration of A.T.P. and absence of creatine phosphate (C.P., another energy-rich phosphate ester in muscle from which the depleted A.T.P. is immediately resynthesized through the Lohmann reaction). Since the A.M. concentration is also very low in these conditions and there is no significant muscle function, A.T.P. is split only slightly and can be resynthesized slowly by other means than through C.P. The presence of a supply of A.T.P., thus maintained, without appreciable contractile activity indicates that this substance is essential not only for the contractile function but also for the "private life," so to speak, of the myometrium. A certain amount of it is obviously required merely to keep the tissue alive.

When during sexual maturation the ovaries become functional and oestrogen production is increased, A.T.P. begins to increase and C.P. appears in significant quantities (Menkes and Csapo, 1952). The same occurs when oestrogen is administered experimentally to ovariectomized animals (Menkes and Csapo, unpublished). The increase of high-energy phosphates in response to oestrogen treatment is much quicker than that of A.M., and their concentration in the muscle reaches a climax while A.M. concentration is still not maximal and function is not yet fully restored. One possible explanation of the early rise of A.T.P. is that it may be involved in the resynthesis of the contractile proteins.

If oestrogen administration is continued, the ~ph will not increase further. These observations seem to be in contradiction to what one would expect when function is maximal. There is, however, another mechanism which takes care of the energy supply of increased function without increase of the concentration of A.T.P., by controlling the turnover of ~ph. As shown by Walaas and Walaas (1950b) and by Borell (1951), using P^{32}, oestrogen increases the turnover of the easily hydrolysable phosphate esters of the uterus. Thus we assume that in the castrated or in the immature animal—that is, in the non-functional uterus—both the final contractile system and the energy-yielding system are quite incomplete. If oestrogen is administered, A.T.P. and the turnover of the high ~ph increase with the simultaneous appearance of C.P. The increase in A.T.P. concentration soon becomes constant while function is still increasing, the extra amount of energy used being compensated for by the increased turnover of ~ph. A similar phenomenon has been observed in our laboratory to occur in the uterus during pregnancy (Menkes and Csapo, 1952). Until the twentieth day of pregnancy in rabbits the easily hydrolysable phosphate fraction of the uterus gradually increases. No further increase, but rather a decrease, can be observed after this period, which coincides with the beginning of a gradual increase in muscle activity and pharmacological reactivity. Thus we must assume that the low concentration of ~ph found after the twentieth day of pregnancy or in oestrus is optimal for maximal function, and the increased use of energy is taken care of by increased turnover of ~ph.

Progesterone, unlike oestrogen, has no activating effect on the uterus of castrates nor a regenerating effect on the final contractile system (Csapo and Corner, 1951). It increases the concentration of the easily hydrolysable phosphate fraction without influencing the A.T.P. concentration. It results, as observed so far, in the accumulation of an unknown compound in this fraction which is neither A.T.P. nor A.D.P. (Menkes and Csapo, unpublished). This effect can be evoked by injected progesterone or by mating (which results in natural progesterone domination through ovulation and corpus luteum formation). It has been shown recently by Walaas (1952) that oestrogens selectively increase the glycogen (and thus the potential ~ph) content of the myometrium of rats and rabbits. The effect is absent in the endometrium and in skeletal muscle and is independent from the blood-sugar level. He concludes that an increased rate of the hexokinase reaction is responsible for increased glycogen formation resulting from oestrogen effect. He found progesterone to be ineffective on the glycogen concentration of the uterus. All these observations indicate that the ovarian hormones affect the energy-yielding system of the uterus, but much more needs to be done before a more complete understanding can be achieved.

Considering the varying concentrations of actomyosin and of high-energy phosphates in various hormonal conditions of the reproductive tract, we ask how these changes alter myometrial function. For the answer we must turn to living muscle and try to explain its behaviour with the

data obtained at the molecular level. A first step in this direction is to observe the relation between actomyosin concentration in the myometrium and the working capacity of the muscle. The most adequate measure of this function is the isometric tension; that is to say, the force developed by contraction of an electrically stimulated strip of muscle that is not allowed to shorten. Thermodynamic studies of Szent-Györgyi (1951) and his associates on frog skeletal muscle have shown that for adequate information on working capacity isometric tension must be studied rather than isotonic amplitude.

One would expect that under well-standardized and optimal conditions the maximum isometric tension which the muscle is able to develop will depend on its actomyosin concentration. Experiments confirm this. After castration the actomyosin concentration and the maximum isometric tension both fall practically to zero and both are restored in similar fashion by administration of oestrogen. The ratio of actomyosin concentration in the oestrous uterus to that of the castrate is 4.6 : 1; the ratio of maximum isometric tension in the two conditions is 4.2 : 1. Progesterone, on the other hand, does not affect either actomyosin concentration or maximum tension (Csapo and Corner, 1953).

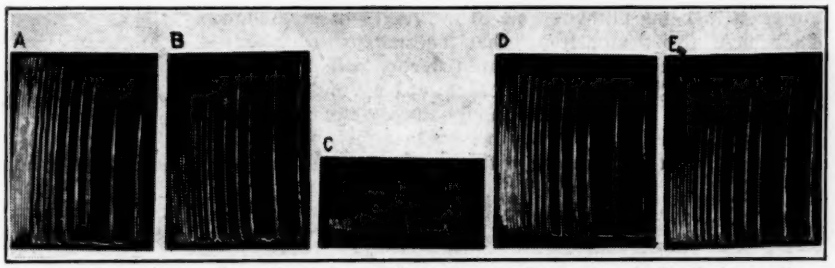

FIG. 1.—Dependence of maximum isometric tension on frequency of stimulation. Electrical stimulation at intervals of ½, 1, 2, and 4 minutes. A, oestrogen-treated castrate; B, castrate treated with oestrogen plus progesterone; C, untreated castrate; D, natural oestrus; E, seven-days pregnancy.

An Unexpected Observation

During the course of our work on isometric tension we made an unexpected observation which we think will help in understanding just how the ovarian hormones act upon the tissue which they affect. The answer to this question being of extreme importance in the physiology of reproduction, we summarize here what we have discovered, although the final proofs are still not available.

It is well established that the function, not only of the myometrium but of all other parts of the reproductive tract, is determined in a final sense by the two ovarian hormones, oestrogen and progesterone (see for literature Reynolds, 1949). Removal of both ovaries results in partial atrophy of the whole reproductive tract, including the myometrium. Castrate atrophy can be avoided, or, if it occurs, the original condition can be restored by the administration of oestrogen to the castrated animal. Special histological and physiological changes functionally adapted to pregnancy are brought about by progesterone.

How the ovarian hormones act upon the tissues to produce these conditions is unknown, and, indeed, the hope of understanding their basic action has been slight because of the great variety of their effects upon various elements of the reproductive tract. It has, however, proved helpful to assume that each ovarian hormone has but one type of effect, which shows itself in different ways in various parts of the reproductive tract because the structure and function of the component cellular elements are different. Moreover, the action of oestrogen and progesterone on a specific tissue, often seemingly opposite or antagonistic, may be fundamentally similar, differing only in the direction of the effect produced. This conjecture rests on a more general assumption about hormone action developed by Dr. Albert Szent-Györgyi (personal communication) from studies of the isolated frog heart, which postulates that hormonal effects are exerted upon the ionic balance of the living cell, and thus the same hormone may similarly affect tissues which are quite different in their organized structure and functions.

Maximum Isometric Tension in Relation to Stimuli

Although in our experiments with the final contractile system we followed the effect of the ovarian hormones down to the molecular level, we do not suppose that their effect actually occurs at this low level of organization and that the hormone directly participates in the individual reactions of which myometrial function is composed. No one, indeed, has ever demonstrated an effect of the sex-gland hormones on any isolated enzyme system, a negative fact which makes it probable that these hormones act at the cellular level, and that their action is to produce favourable or unfavourable conditions for a set of reactions taking place in the cell. Our experiments so far indicate, though they do not as yet completely prove, that the effect of the ovarian hormones on the myometrium is accomplished by alteration of the potassium balance of the myometrial cells. The new observation from which this conclusion stems is that the maximum isometric tension which a strip of uterine muscle can develop depends on the rate at which successive stimuli are applied. If the rate of stimulation is varied from once every half-minute to once in four minutes, the oestrogen-dominated uterus exhibits a decrease in tension with decreasing rate of stimulation (Fig. 1), whereas the progesterone-dominated uterus increases its tension as the intervals become longer. This difference occurs not only in castrates treated with the respective hormones but also in intact animals under natural conditions—that is, in oestrus and pregnancy. Whether the hormone is supplied by the animal's own ovaries or by infection, the effect is the same. It should be added that the castrate uterus is insensitive to changes in rate, its weak isometric contractions developing the same tension regardless of the intervals.

It is surprising to see that the progesterone-dominated uterus, which completes a single isometric contraction cycle in shorter time than the oestrogen-dominated muscle, requires more rest between two stimuli in order to develop maximum tension. Return to zero tension, therefore, does not indicate complete recovery of the contractile system as a whole in the progesterone uterus. We first believed that the incomplete resynthesis of ~ph was responsible for the unique behaviour in this hormonal condition. This possibility can still not be completely disregarded in view of the active sodium transport, which may overlast the contraction cycle and which uses a considerable amount of energy (Steinbach, 1952). The suggestion of Ling (1952) also has to be considered, that high-energy phosphates influence muscle function not only because of their stored energy but also because of their high-valency negative charges, which participate in linking cations to the contractile proteins. Their concentration, therefore, will partly determine the cation gradient between the outside and the inside of the cell on which the resting potential depends. A more direct explanation results from the realization that the effect we have been discussing is quite similar to the well-known staircase phenomenon of heart muscle.

Hajdu and Szent-Györgyi (1952) have recently studied the Bowditch phenomenon of the frog heart under isometric conditions, varying the frequency of stimulation in a "steady state." They find that the steep slope of the staircase that develops in regular Ringer–Conway solution can be completely abolished if the potassium concentration of the perfusion fluid is decreased to one-eighth of the usual level.

Referring to the data of Fenn (1937) and Fenn and Cobb (1936), who found that contraction entails a loss of potassium, they assumed that the resting frog heart contains more intracellular potassium than is optimal for the development of maximum tension, and therefore the heart must be stimulated very frequently to exclude the supra-optimal amount of potassium and keep it out. If stimulation is discontinued, intracellular potassium accumulates, the staircase reoccurs, and the tension drops. This effect can be abolished by decreasing the potassium outside, the increasing gradient being unfavourable to the return of potassium. They have also demonstrated that the staircase disappears at 0° C., whereas its slope becomes steeper with increasing temperature. Serum, desoxycorticosterone, and digitalis glucosides have the same effect as the decrease of potassium in the perfusion Ringer. They believe that these substances inhibit the return of potassium to the cell.

The Uterine Staircase

We have shown that the uterus of a castrate rabbit exhibits no staircase if stimulated with constant frequency after a period of rest (Fig. 2). This suggests that the phenomenon is not a fixed characteristic of the myometrium, but rather an expression of the dominant hormonal effect. The oestrogen - dominated uterus has a similar staircase to that of the frog heart, as first observed by Bowditch, whereas the progesterone-dominated uterus behaves in an opposite manner —that is, it has a staircase sloping in the reverse direction, which will be designated as "negative staircase" in contrast to the regular or "positive staircase" (Csapo and Corner, 1952).

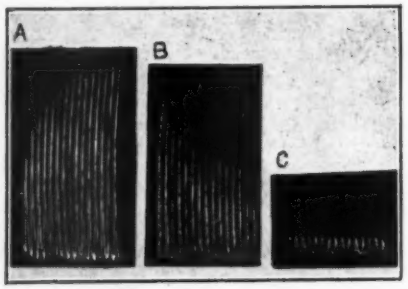

FIG. 2.—Uterine staircase. Maximum isometric tension developed upon stimulation at intervals of 1 minute, beginning after 10 minutes' rest. Castrated mature virgin rabbits; A, treated with oestrogen; B, oestrogen plus progesterone; C, untreated.

One would expect to see slopes intermediate between the extreme positive and negative staircase if the two hormones are simultaneously administered in various proportions. Experiments have shown this to be the case. For this and similar studies in which quantitative precision is important the frequency of stimulation has to be varied in an otherwise steady state.

The staircase was found to be most negative in early pregnancy. This condition can be imitated in the castrate only if after three days' oestrogen treatment progesterone is administered without oestrogen, a fact which suggests that the latter is not present during the first few days of pregnancy. By the administration of oestrogen during early pregnancy we expected, therefore, to produce a levelling effect on the negative slope of the staircase and also a disturbance of pregnancy. We found that a single dose of 5 μg. of oestrogen per 4 kg. body weight, administered between the second and fifth days of pregnancy, significantly reduces the slope of the negative staircase and completely abolishes pregnancy (Csapo, 1953).

Effect of Temperature and the Potassium-sodium Ratio

Inasmuch as the staircase so accurately reveals the delicate balance of the ovarian hormones, it is important to learn its nature. In agreement with Hadju and Szent-Györgyi's observation (1952), we found that the positive staircase of the oestrogen uterus disappears at low temperature (Fig. 3), whereas its slope increases with increasing temperature. On the other hand, the negative slope of the

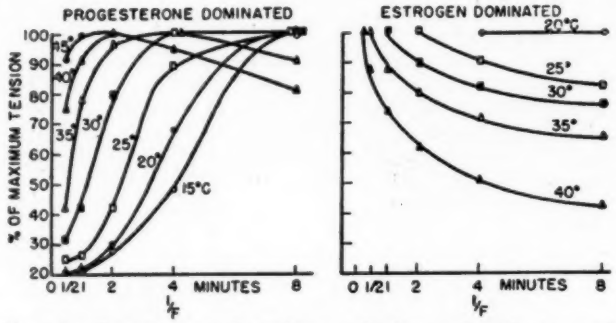

FIG. 3.—Temperature dependence of slope of staircase and negative staircase.

staircase of the progesterone uterus decreases with increasing temperature. Like the frog heart, the oestrogen uterus exhibits an increase in tension within about two minutes if the potassium–sodium ratio is decreased in the bath. The staircase does not disappear, however; its slope is only slightly reduced. If the tissue is subjected to repeated washing for half-hour periods in potassium-free Krebs solution, a gradual decrease in the slope of the staircase can be observed, with a complete disappearance of the staircase after about two hours' treatment, but at the same time the tension also decreases gradually (Csapo, 1953).

If the oestrogen uterus is kept in potassium-free Krebs solution as before and the perfusion fluid is then changed to normal Krebs solution, the potassium–sodium ratio thus being suddenly increased, and if the muscle is stimulated once every half-minute, the tension drops and remains at the low level for about 20 minutes, increasing slowly thereafter. If during this short period of time the staircase is observed a negative slope appears. Thus this rather drastic treatment results in behaviour of the oestrogen uterus similar to that of the progesterone uterus. It is a transitory effect, however, and after the 20 minutes the staircase is positive again (Csapo, 1953).

The effect of alterations in temperature and potassium–sodium ratio can be more easily observed with the progesterone-dominated uterus (Fig. 4). Increase of either

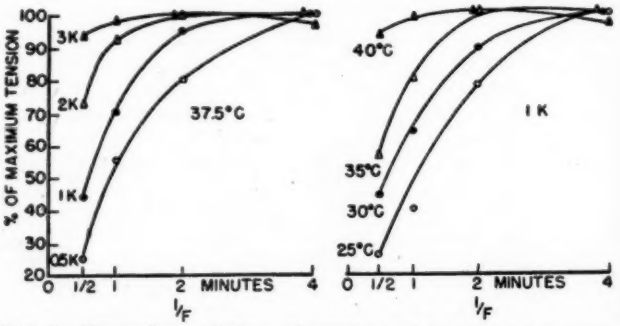

FIG. 4.—Dependence of slope of negative staircase upon potassium concentration and temperature.

temperature or the external potassium–sodium ratio results in gradual disappearance of the negative staircase. At sufficiently high potassium–sodium ratio outside (about fourfold increase in potassium concentration of the original Krebs solution), the negative slope of the staircase with the progesterone uterus not only disappears but there is a slight positive slope, such as is characteristic of the oestrogen uterus. Thus by alterations in the potassium concentration of the perfusion fluid the characteristic behaviour of oestrogen and progesterone uteri with respect to the slopes of their respective staircases can be more or less completely reversed (Csapo, 1953).

A striking difference in the behaviour of oestrogen and progesterone uteri with respect to maximum tension also appears if the potassium–sodium ratio outside is gradually increased (Fig. 5). The oestrogen uterus exhibits a gradual

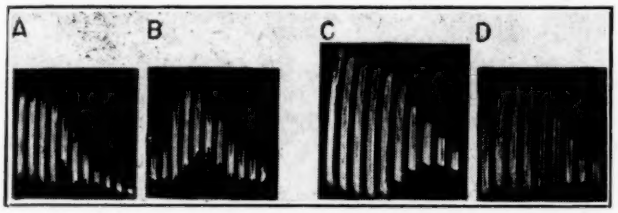

FIG. 5.—Dependence of maximum isometric tension upon potassium concentration. Each bar represents a group of four contractions in response to stimulation at ½-minute intervals. The K concentration is raised in each group from left to right, from standard or half-standard K concentration of Krebs solution, to 2×, 3×, . . . 10×K. A, castrate treated with oestrogen; B, castrate treated with oestrogen plus progesterone; C, as A; D, strip from same uterus as C, but after 24 hours' storage at 0° C. in Krebs solution of standard K concentration. Note resemblance to B.

decrease in maximum tension with increasing potassium–sodium ratio, whereas the progesterone uterus shows the opposite behaviour up to a threefold increase in the potassium concentration over the original Krebs solution. If the oestrogen uterus is subjected to storage it loses its characteristic behaviour and exhibits a pattern similar to that of the progesterone uterus (Csapo, 1953).

The duration of a single isometric contraction cycle is also greatly dependent on temperature and on the external potassium–sodium ratio. In general, a decrease in temperature increases the duration of both oestrogen and progesterone uteri, but the former has a much greater temperature dependence. Decrease in the potassium-sodium ratio outside increases the duration of the contraction of the oestrogen uterus and steepens the ascending phase of the isometric contraction cycle. The progesterone uterus has no change in duration under similar experimental conditions (Csapo, 1953).

Conclusions

From these experiments one can conclude that oestrogen and progesterone alter myometrial function in opposite directions, as revealed by measurements of the maximum isometric tension. Their effect can be counteracted or even reversed *in vitro* by changing the temperature or the potassium concentration of the perfusion Krebs solution. Whether a different intracellular potassium concentration exists in the uterus *in vivo* in the two contrasting hormonal conditions or as a result of the alteration of the potassium concentration in the perfusion fluid, we cannot say as yet, because we do not know the extent of the extracellular space in the uterus. It is possible that not the absolute quantities of the respective ions, but rather the dynamics of their movements, are changed. If the intracellular potassium concentration is changed as a result of hormonal action, the question ought to be considered whether a change in the distribution of other ions occurs simultaneously as a consequence of this alteration or as an independent effect.

The demonstrated *in vitro* effect of the potassium ion on the myometrial cell cannot be discussed in any detail at present, because the system in which the experiments have been performed is too complex. Hajdu and Szent-Györgyi (1952) proposed that alterations in the potassium balance of the muscle cell directly affect the contractile protein, actomyosin. The effect of potassium is, however, probably more complex. Its extreme importance in activating enzyme reactions, especially those involved in the glycolytic sequence of rabbit skeletal, cardiac, and uterine muscle, has been recently emphasized by Boyer (1953). We know from Walaas's work (1952) that oestrogen controls glycogen formation in the myometrium, perhaps through the hexokinase system. Thus we have to consider, as one possibility, that the ovarian hormones, through their alteration of the potassium balance of the myometrium, will modify the activity of specific enzyme systems, especially those involved in cellular energetics. Ling (1952) has shown that A.T.P., C.P., and hexosephosphates occupy key positions in muscle function not only because of their stored energy but also because of their high-valency negative charges which link cations (especially potassium) to the contractile and other proteins of the muscle cell. Their concentration therefore determines not only the amount of energy which can be spent immediately during activity but also the gradient of cations between the outside and the inside of the cell, which in turn determines the resting potential of the cell. Thus we see that a change in the potassium balance of the myometrium evoked by the action of the ovarian hormones might easily modify a whole series of intracellular reactions, thus producing great variations in function of the organ as a whole.

This concept may ultimately not only explain the "pregnancy reversal" described 45 years ago by Sir Henry Dale but also provide a key to many other problems of uterine physiology and hormone action.

REFERENCES

Athias, M. (1919). *J. Physiol. Path. gén.*, **18**, 731.
Blair, E. (1923). *Amer. J. Physiol.*, **65**, 223.
Borell, U. (1951). *Acta endocrinol., Kbh.*, **8**, 131.
Boyer, P. D. (1953). *Potassium Symposium*, Minneapolis. In press.
Corner, G. W. (1923). *Amer. J. Anat.*, **32**, 345.
Csapo, A. (1948). *Nature, Lond.*, **162**, 218.
—— (1949). *Acta physiol. scand.*, **19**, 100.
—— (1950a). *Amer. J. Physiol.*, **160**, 46.
—— (1950b). Ibid., **162**, 406.
—— (1953). *Potassium Symposium*, Minneapolis. In press.
—— and Corner, G. W. (1951). *Endocrinology*, **49**, 349.
—— —— (1952). *Endocrinology*, **51**, 378.
—— —— (1953). *Science*, **117**, 162.
—— Erdös, T., Naeslund, J., and Snellman, O. (1950). *Biochim. biophys. Acta*, **5**, 53.
—— and Gergely, J. (1950). *Nature, Lond.*, **166**, 1078.
—— and Herrmann, H. (1951). *Amer. J. Physiol.*, **165**, 701.
Cushny, A. R. (1907). *J. Physiol.*, **35**, 1.
Dale, H. H. (1907). Ibid., **34**, 163.
Engelhardt, W. A., and Ljubimowa, M. N. (1939). *Nature, Lond.*, **144**, 668.
Fenn, W. O. (1937). *Amer. J. Physiol.*, **119**, 307.
—— and Cobb, D. M. (1936). Ibid., **115**, 345.
Hajdu, S., and Szent-Györgyi, A. (1952). Ibid., **168**, 159.
Kehrer, E. (1907). *Arch. Gynäk.*, **81**, 160.
—— (1908). *Arch. exp. Path. Pharmak.*, **58**, 366.
Keye, J. D. (1923). *Bull. Johns Hopk. Hosp.*, **34**, 60.
Knaus, H. (1930). *Arch. Gynäk.*, **141**, 374. (See for references to a series of papers by this author.)
Ling, G. N. (1952). *Phosphorus Metabolism*, **2**, 748. Baltimore.
Lohmann, K. (1938). *Ann. Rev. Biochem.*, **7**, 125.
Makepeace, A. W., Corner, G. W., and Allen, W. M. (1936). *Amer. J. Physiol.*, **118**, 376.
Menkes, J. H., and Csapo, A. (1952). *Endocrinology*, **50**, 37.
Mommaerts, W. F. H. M. (1950). *Muscular Contraction*. New York.
Needham, D. (1952). *Advanc. Enzymol.*, **13**, 151.
Reynolds, S. R. M. (1931). *Amer. J. Physiol.*, **97**, 706.
—— (1949). *Physiology of the Uterus*, 2nd ed. New York.
—— and Allen, W. M. (1932). *Amer. J. Physiol.*, **102**, 39.
Robson, J. M. (1936). *J. Physiol*, **88**, 100. (See for references to a series of papers by this author.)
Snellman O., and Erdös, T. (1948a). *Biochim. biophys. Acta*, **2**, 650.
—— —— (1948b). Ibid., **2**, 660.
Steinbach, H. B. (1952). *Proc. nat. Acad. Sci., Wash.*, **38**, 451.
Stickel, M. (1913). *Arch. Physiol.*, p. 259.
Szent-Györgyi, A. (1945). *Acta physiol. scand.*, Suppl. 25, **9**, 1.
—— (1947). *The Chemistry of Muscular Contraction*. New York.
—— (1951). Ibid., 2nd ed. New York.
Van Dyke, H. B., and Gustavson, R. G. (1929). *J. Pharmacol.*, **37**, 379.
Walaas, O (1952). *Acta endocrinol., Kbh.*, **10**, 175.
—— and Walaas, E. (1950a). *Acta physiol. scand.*, **21**, 1.
—— —— (1950b). Ibid., **21**, 18.
Weber, H. H. (1935). *Pflügers Arch. ges. Physiol.*, **235**, 205.

The *Journal de Génétique Humaine*, a new quarterly publication, is intended for doctors, biologists, anthropologists, and others interested in problems related to heredity. Its editorial board comprises Professor A. Franceschetti (Geneva), Professor L. van Bogaert (Antwerp), and Professor M. Lamy (Paris). The journal is published by Editions Médecine et Hygiène, 15, Boulevard des Philosophes, Geneva, and the subscription is 30 Swiss francs (£2 10s.) per annum.

A SURVEY OF PRESCRIBING IN SCOTLAND IN 1951

BY

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A survey of 17,301 prescriptions issued on Form E.C.10 in England in 1949 (Dunlop *et al.*, 1952) provided an incentive to a further and more extended investigation of prescribing, and in addition indicated how a subsequent study could be planned in order to give more varied and statistically valid information, and to avoid some of the errors to which our attention was drawn in the previous paper. Scotland was chosen as the area to be surveyed, as it formed a manageable unit and represented all types of medical practice.

Material and Method

The material consisted of an approximately 1% sample of all E.C.10 forms issued in each of the 25 executive council areas in Scotland during the month of October, 1951. There were 13,340 of such forms, which included a total of 18,848 prescriptions. Except for a few minor changes the method of tabulation and sorting was similar to that adopted in our previous survey of English prescriptions. Nevertheless, since the method of selection was different and since the present survey follows the previous one after an interval of two years, no very close comparison can be made between the results of the two surveys. It will be seen, however, that on the whole the frequency with which different drugs are ordered and the form in which they are prescribed are not dissimilar in England and Scotland.

In addition to the E.C.10 forms all the E.C.10A forms (stock order forms) for the same month of October were scrutinized. Their total number was 1,569. In Scotland such forms are used by practitioners to order drugs and appliances which they personally administer.

Results

That the orders on E.C.10A forms comprised only an insignificant part of the cost of the total prescriptions is indicated by the following figures:

	£
Total cost of orders on Form E.C.10A in Scotland in October, 1951	8,500
Total cost of prescriptions on Form E.C.10 in Scotland in October, 1951	412,500

Thus the cost of orders on Form E.C.10A comprised only about 2% of the total prescribing costs, and involved an average yearly expenditure per practitioner of £42 10s. About 45% of the orders on these forms were for dressings and appliances.

A study of the E.C.10A forms revealed only a small number of lavish and extravagant orders, though a total of 200 ml. of a proprietary liver extract on one form seemed hard to justify. Over 7 tons (7,112 kg.) of cotton-wool are ordered yearly on E.C.10A forms alone. Though the figure seems formidable, it represents a yearly consumption of rather less than 6½ lb. (2.9 kg.) per doctor.

The figures in Tables I and II have been grouped under the five Scottish regions. In addition those pertaining to the four main cities have been extracted separately. Even with this grouping a considerable variation in the average number of patients per practitioner (list size) and in the number of E.C.10 forms issued per unit (1,000 persons) of population is apparent, and the proportion of E.C.10 forms

TABLE I

	Western Region (Excluding Glasgow)	Glasgow City	S-eastern Region (Excluding Edinburgh)	Edinburgh City	Eastern Region (Excluding Dundee)	Dundee City	N-eastern Region (Excluding Aberdeen)	Aberdeen City	Northern Region
Population	1,740,200	1,093,276	643,192	465,913	223,879	177,890	316,754	181,923	173,912
No. of prescriptions analysed	6,364	4,959	2,237	1,732	633	667	1,066	780	420
E.C.10 forms per 1,000 population	248	311	252	257	212	264	246	312	182
Average list size	2,270	2,078	2,290	1,801	1,930	2,069	1,720	2,220	1,510

TABLE II.—*Principal Types of Prescription and Groups of Drugs Prescribed*

	Percentage of Total Prescriptions								
	Western Region Excluding (Glasgow)	Glasgow City	S-eastern Region (Excluding Edinburgh)	Edinburgh City	Eastern Region (Excluding Dundee)	Dundee City	N-eastern Region (Excluding Aberdeen)	Aberdeen City	Northern Region
Proprietary	32·8	31·6	28·8	28·3	31·4	27·4	35·5	27·4	36·5
Tablets	32·6	30·6	36·0	34·5	36·5	30·3	34·6	35·0	39·3
Mixtures	28·8	32·6	26·0	26·7	29·7	32·6	28·7	28·7	28·4
Skin preparations	14·6	14·4	13·6	14·8	11·5	13·8	11·3	13·3	9·6
Dressings	10·1	9·8	12·0	10·3	8·2	11·5	9·8	9·9	9·1
Powders	4·4	3·7	3·4	3·7	2·8	4·9	4·4	3·7	3·1
Eye, ear, nose	3·5	3·2	3·6	4·6	3·3	3·0	4·1	4·9	3·3
Injections	2·8	2·1	2·8	2·0	3·6	1·8	3·1	1·8	4·8
Gargles	1·7	2·3	1·5	1·9	3·0	1·0	2·1	1·8	0
Barbiturate	9·9	9·6	9·3	11·0	10·7	8·5	10·6	10·5	13·1
Bromide	1·1	1·2	0·9	0·5	1·7	1·5	1·1	1·0	1·0
Mild analgesic	9·0	10·6	10·3	9·3	9·2	10·9	10·1	9·0	8·2
Cough preparation	8·5	10·0	8·4	8·7	8·2	10·1	7·7	12·4	4·8
Stomachic	7·9	7·3	5·7	6·5	5·7	9·0	8·4	5·1	11 3
Antispasmodic	7·0	6·8	5·9	6·7	7·0	4·8	7·3	7·8	5·3
Sulphonamide	5·7	6·6	5·6	6·8	6·3	7·0	4·7	5·6	5·8
Antibiotic	5·4	5·2	4·4	4·7	4·1	4·3	4·9	5·1	5·5
Vitamin	5·0	5·6	5·1	4·9	6·6	4·5	5·8	3·4	6·2
Tonic	4·5	4·5	3·0	3·7	3·8	4·9	3·6	3·6	3·9
Antihistamine	4·3	2·9	3·0	3·6	3·2	3·4	3·3	4·1	5·5
Iron	3·3	3·0	3·0	3·3	3·2	3·1	2·4	3·1	2·9
Laxative	2·1	2·1	2·8	2·0	4·0	2·7	2·4	3·0	2·1
Strong analgesic	1·8	2·8	2·0	2·6	2·2	1·8	1·8	2·1	2·2
Amphetamine	2·0	1·8	2·1	1·7	1·3	1·5	1·9	1·8	0·5

issued per unit of population seems to vary according to the population density of the area. The significance of this finding is discussed later.

Vitamins, tonics, and symptomatic remedies (sedatives, hypnotics, analgesics, cough mixtures, stomachics, and laxatives) constituted 51.6% of all prescriptions written. A large proportion of these drugs must be prescribed as placebos. They are often relatively cheap in themselves, yet the total cost of compounding and packing them is relatively enormous. Thus, if the cost of prescriptions to the State is to be diminished it must be directed to a reduction of these symptomatic remedies as well as to extravagant prescriptions of expensive drugs to which so much attention has been directed in the past.

The general pattern of prescribing was similar to that found in the earlier English survey, but the following points seem worthy of emphasis because of their dissimilarity or of reiteration because of their importance.

As was to be expected after a lapse of two years, there was some increase in the prescription of newer drugs such as the antibiotics and the antihistamines. In Scotland, however, the prescription of the amphetamines was not significantly more frequent than it had been in England two years previously—a somewhat surprising finding in view of the Pricing Bureau's figures for 1952.

The variation in the proportion of proprietary preparations prescribed in the different areas was not great, but the overall proportion (30%) is considerably higher than the corresponding figure (21%) in the previous survey. An accurate comparable English figure for 1951 was not available to us, but this suggests that the tendency to prescribe proprietary medicines is either increasing generally or is greater in Scotland than in England.

It is satisfactory to note that bromides were prescribed alone very rarely (1%) compared with the previous English figure of 5.8%. Bromides seldom prove more effective than phenobarbitone either as sedatives or as anticonvulsants. Their frequent side-effects and the undesirable cumulative toxic effects which result from their prolonged administration relegate bromides to the group of drugs which should largely be discarded in modern therapeutics. Bromides, however, were prescribed with chloral hydrate on 40 occasions, representing some 4,000 of such prescriptions in Scotland in October, 1951. It seems unfortunate that this mixture should appear in the *National Formulary* for 1952, for bromides are sedatives which have to be administered frequently before there is a sufficient replacement of chloride by bromide ion to exert a depressant effect on the central nervous system, and their occasional administration with a hypnotic such as chloral has no more effect than a dose of salt water.

Compound cough mixtures containing sedatives and expectorants were ordered as often as sedative preparations, but purely expectorant cough mixtures were not ordered as often as either. This is satisfactory, as there is considerable doubt about the value of expectorants, which were found to be very commonly prescribed in the English survey.

The proportion of prescriptions for cough mixtures was higher in the urban than in the rural areas. This was particularly noticeable in the case of Aberdeen City (12.4%) in comparison with the remainder of the North-eastern Region (7.7%). Such figures seem to indicate that coughs are one of the hazards of city as opposed to country life, and support is given to this hypothesis by the mortality figures for respiratory disease in the Registrar-General's report. On the other hand, there was no constant similar trend in the proportion of prescriptions for stomachics in town and country, which does not support the general impression that dyspepsia is also one of the penalties of urban life.

As in the previous survey, vitamins were prescribed more often than iron, and constituted about 5% of all prescriptions. The actual number of prescriptions for vitamins in the 1% sample of prescriptions analysed was 976—that is, approximately 97,600 for the month of October in Scotland, or over one million for the year. When it is remembered that the average prescription on Form E.C.10 costs the country over 4s., and that vitamins are often relatively expensive drugs, a very conservative estimate of the cost of vitamin prescriptions in Scotland for the year is £230,000. As the population of Scotland is about one-ninth that of the United Kingdom it might be argued that the bill for vitamin prescriptions alone in Britain is at least £2,000,000. This estimate is intentionally a very conservative one, since, as will be seen later, the number of prescriptions issued in October happened to be above average. That, the figure

TABLE III

	No. of Registered Patients	No. of Doctors	Scripts Issued 1951					
			July	August	September	October	November	December
Western hospital region:								
City of Glasgow	1,093,276	526	224,923	258,486	279,743	339,656	327,146	286,412
Argyll and Bute (counties of)	75,709	61	14,969	14,284	13,644	14,916	14,421	13,056
Ayr (and county of)	313,134	139	66,635	66,880	70,546	79,478	77,907	71,468
Dumfries (and county of)	82,552	38	18,004	18,287	18,874	22,578	21,698	19,985
Dunbarton (county of)	156,303	62	31,124	34,562	36,033	44,192	42,928	37,869
Galloway (Kirkcudbright and Wigtown (and counties of))	59,335	34	10,084	10,420	10,635	11,545	11,407	10,795
Lanark (and county of)	512,530	205	104,940	109,366	118,335	139,910	137,154	122,710
Renfrew (and county of)	322,626	136	60,934	60,491	65,823	80,068	77,591	65,059
Stirling and Clackmannan (and counties of)	218,011	92	44,865	45,162	49,177	58,520	57,607	52,347
South-eastern hospital region:								
City of Edinburgh	465,913	259	89,586	87,649	93,323	119,840	116,602	101,233
Fife (county of)	301,776	123	69,052	69,817	73,368	83,960	82,399	76,650
Lothians and Peebles (and counties of)	249,457	106	45,641	47,669	49,427	57,212	55,333	51,208
Roxburgh, Berwick, and Selkirk (and counties of)	91,959	52	17,366	17,227	18,014	20,999	20,714	19,642
Eastern hospital region:								
City of Dundee	177,890	86	32,589	36,989	39,745	46,849	47,110	43,638
Angus (county of)	93,018	43	18,179	18,140	19,574	21,478	21,870	21,328
Perth and Kinross (and counties of)	130,861	73	22,103	22,169	23,919	26,025	26,673	24,630
North-eastern hospital region:								
City of Aberdeen	181,923	82	44,261	45,339	43,309	57,070	56,221	53,304
Aberdeen and Kincardine (counties of)	171,968	87	34,561	35,663	36,406	39,068	37,402	38,261
Banff and Moray (counties of)	104,831	65	29,116	30,072	31,395	32,726	33,037	33,027
Orkney (county of)	20,792	18	3,681	3,409	3,797	4,289	4,184	4,067
Zetland (county of)	19,163	14	2,223	2,247	2,250	2,200	2,520	2,668
Northern hospital region:								
Inverness (and county of)	78,743	53	11,418	11,753	11,305	12,618	12,439	11,546
Caithness (county of)	22,416	11	3,894	3,865	4,002	4,351	4,126	4,316
Ross and Cromarty (counties of)	59,401	40	9,980	9,957	10,599	10,938	11,762	11,572
Sutherland (and county of)	13,352	11	1,976	2,085	2,038	2,298	2,118	2,079

is not an overestimate can be deduced from the fact that vitamins account for at least 5% of the total annual expenditure on drugs, which was well over £40,000,000 in 1951, giving a figure in excess of £2,000,000. It is probable that only a very small proportion of the vitamin prescriptions representing this vast sum serve any very useful purpose, especially as cod-liver oil and orange juice for babies and expectant mothers are issued at antenatal and child welfare centres and do not appear on Form E.C.10. When it is recalled that, owing to the present financial position of the country, health centres cannot be built and that all hospital boards are being faced with serious difficulties as regards the staffing and general administration of their hospitals, these figures applied to vitamins alone, quite apart from other placebo prescriptions, deserve serious consideration.

In the English survey it was noted that liver extracts were ordered 50 times, in comparison with only 68 prescriptions for insulin. As the megaloblastic anaemias are relatively uncommon in comparison with diabetes mellitus it was concluded that liver extract was often used for its questionable general tonic rather than for its haemopoietic properties or for anaemias other than megaloblastic, for which it could be of no service. The present survey gave even more striking figures in this respect, for it showed that liver extract was ordered 125 times, in comparison with only 97 prescriptions for insulin and 134 for digitalis. Further, folic acid was ordered 32 times. When it is recalled that this drug should be used only in tropical sprue and in some rare cases of megaloblastic anaemia, such as the megaloblastic anaemias of the malabsorption syndrome and pregnancy, and that it is absolutely contraindicated in pernicious anaemia, some 3,000 prescriptions for it a month in Scotland would seem to be excessive.

It has been suggested from time to time by lay members of executive councils that quantities of expensive toilet requisites are commonly prescribed on Form E.C.10. This survey did not suggest that there was any justification for such strictures.

Factors Influencing Prescription Rates

The interest of these various findings should not divert attention from the more fundamental fact, demonstrated in Table I, that there is a remarkable variation between the different areas in the number of scripts (E.C.10 forms) issued per unit of population, although there is generally not much variation in the type of drug prescribed (Table II). It was realized that the figures for October alone might not give a truly representative picture of prescribing practice. Consequently the information shown in Table III for the months of July to December, 1951, inclusive was obtained. It will be noted that the number of scripts issued in October, which was chosen fortuitously for the detailed survey, was actually considerably higher than in the other months. The data collected in Table III are analysed in Table IV and in Figs. 1, 2, and 3.

Table IV suggests that there is a relationship between the script rate and the population density, though the position of Banff at the head of the list is inexplicable. The figures for population density do not take into account the uneven distribution of the population over the areas concerned. Thus in Lanarkshire there is a highly industrialized portion in the north, where the population is of almost urban density, while the remainder of the county is agricultural and sparsely populated. The same considerations apply to Fife, Dunbarton, Dumfries, and Stirling, and account for their apparently incongruous position in the Table. That there is nevertheless a definite statistical relationship between script rate and population density is obvious from Fig. 1.

Fig. 2 shows that the script rate varies with list size, and it can also be demonstrated that there is a statistical correlation between list size and population density. There is thus an intimate interrelationship between these three factors —script rate, population density, and list size.

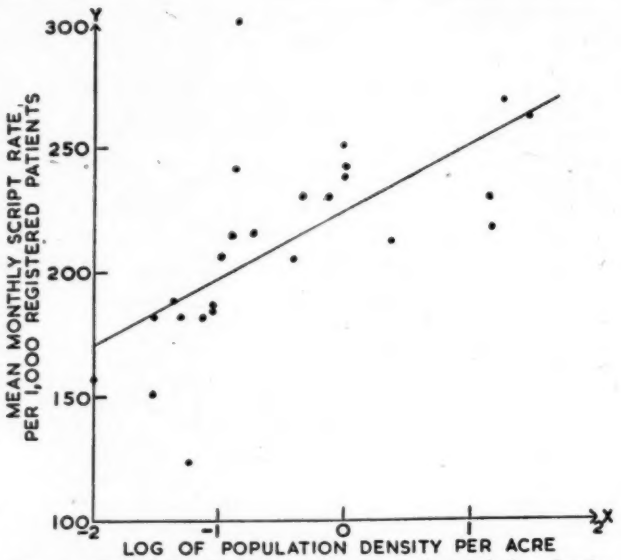

FIG. 1.—Correlation between script rate and population density. ($Y=225.1+26.9X$; $r=0.617$; $P<1\%$, d.f. 23.)

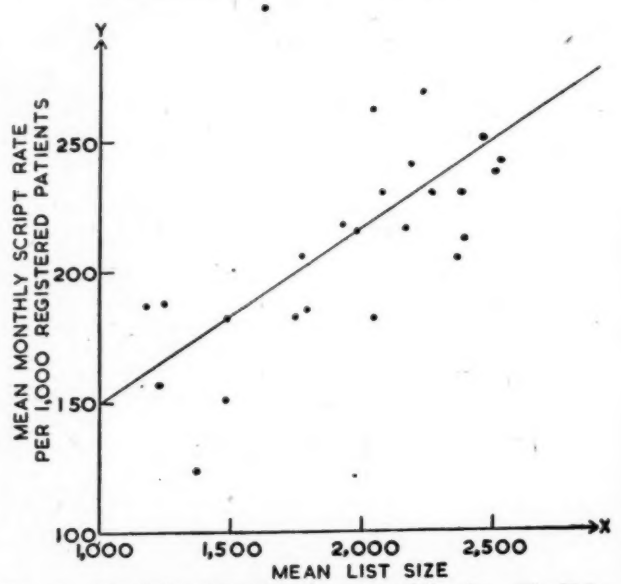

FIG. 2.—Correlation between script rate and list size. ($Y=83.3+0.0667X$; $r=0.7$; $P<1\%$, d.f. 23.)

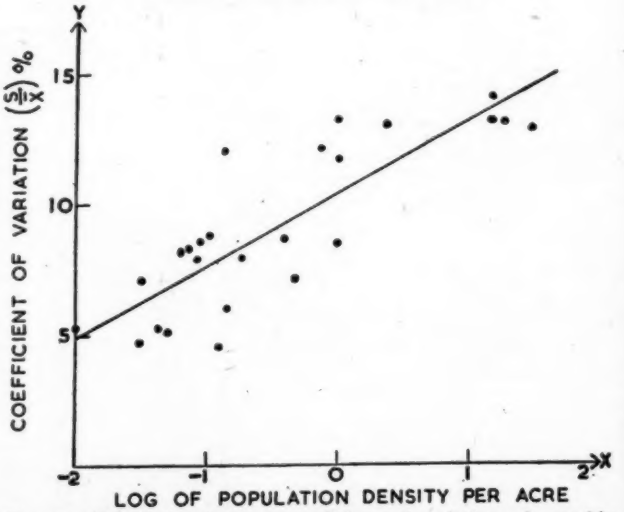

FIG. 3.—Correlation between coefficient of variation of monthly script rates with population density. ($Y=10.44+2.75X$; $r=0.83$; $P<1\%$, d.f. 23.)

TABLE IV

Executive Council Area	Mean Monthly Script Rate per 1,000 Population July–December, 1951 (and Standard Deviation)	Population Density per Acre	Average List Size
Banff*	301 (18)	0·14	1,614
Aberdeen ..	269 (35·2)	17·47	2,220
Glasgow	262 (33·6)	28·21	2,078
Fife	251 (20·7)	0·96	2,455
Dunbarton ..	242 (32·2)	1·06	2,520
Dumfries	241 (28·9)	0·13	2,180
Lanark	238 (27·8)	0·98	2,500
Stirling	230 (27·7)	0·70	2,370
Dundee	230 (32·4)	14·57	2,069
Ayr	230 (16·4)	0·45	2,255
Edinburgh ..	218 (28·4)	14·42	1,801
Angus	216 (18)	0·18	2,165
Aberdeen county	215 (9·8)	0·12	1,977
Renfrew	212 (27·7)	2·27	2,375
Roxburgh ..	206 (18·1)	0·10	1,769
Lothians	205 (17·9)	0·38	2,355
Argyll	188 (10)	0·04	1,240
Orkney	187 (16·1)	0·09	1,175
Perth	185 (14·6)	0·08	1,792
Ross	182 (12·9)	0·03	1,480
Galloway ..	182 (15·1)	0·07	1,742
Caithness ..	182 (9·3)	0·05	2,038
Sutherland ..	157 (8·3)	0·01	1,214
Inverness	151 (7)	0·03	1,484
Zetland	123 (10)	0·06	1,370

* See text.

The correlation between script rate and population density is an overall relationship, since associated with population density, though not necessarily dependent upon it, are such factors as the availability of the doctor, differential morbidity, the psychological attitude of the patient to disease, and the list size. Thus in urban areas the practitioner is usually conveniently available for a consultation and a prescription, often for very trivial maladies, in contrast to the Highlands and Islands of Scotland, where moor and fen, crag and torrent, and even stormy seas may intervene between the patient and doctor. Secondly, there may be an increased morbidity in the urban as opposed to the country population. Respiratory disease, as has been noted, is an obvious example. Thirdly, as Ferguson (1945) has suggested, the industrial population, perhaps because of family tradition, trade union example, habit, and economic pressure, are possibly more likely to declare themselves unfit for work than the rural population. To a bored, disinterested workman, with an unpleasant job in squalid surroundings and in the company of uncongenial associates, a very minor disability may perhaps be a welcome pretext to absent himself from work, and prescriptions follow.

Lastly, list size has been implicated as a cause for a high script rate, and this is suggested by Fig. 2. The overworked practitioner with an excessive number of visits to make and an inflated attendance at his surgeries may well find that it takes a long time to get a full history and to make a complete clinical examination, but only a short time to write a prescription. Nevertheless it will be readily understood that script rate may be related to list size simply because the latter depends upon population density. To assess accurately the significance of list size on script rate it would be necessary to obtain the figures for script rate in large as opposed to small practices among populations of similar density, but this information is not available. By an indirect approach, however, some evidence can be obtained to suggest that list size is not at any rate the sole factor involved, and probably not the most important one.

Table III shows a considerable monthly variation in the number of scripts issued in each area, and it is apparent that the degree of variation tends to be greater where the population is dense. There can be no doubt about the significance of the correlation shown by plotting the coefficient of variation against the population density (Fig. 3). This implies that the seasonal variation is relatively greater in densely populated areas. It is improbable that this can be entirely attributable to list size, and it is more likely to be due to other factors. If among these other factors the availability of the doctor and the psychological attitude of the industrial worker towards disease are, as has been suggested, important, then the 1s. charge on prescriptions, which has been instituted since 1951, may be justifiable as a mild mass deterrent, though it is unfortunate that it penalizes the chronic sick without greatly discouraging the hypochondriac with a passion for medicine.

Summary

A survey has been made of 18,848 prescriptions on Form E.C.10 and of 1,569 E.C.10A forms issued in Scotland during the month of October, 1951, and the general pattern of prescribing has been analysed and reviewed.

In an attempt to elucidate the factors determining prescribing rates the number of scripts issued in the 25 executive council areas in Scotland in the months of July to December inclusive was contrasted with the population density and the average list size. A considerable degree of correlation was established, and the factors concerned are discussed.

REFERENCES

Dunlop, D. M., Henderson, T. L., and Inch, R. S. (1952). *British Medical Journal*, 1, 292.
Ferguson, T. (1945). *Edinb. med. J.*, 52, 252.

URINARY EXCRETION OF THE PRESSOR AMINES IN RELATION TO PHAEOCHROMOCYTOMA

BY

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The presence of adrenaline-like substances in human urine has acquired importance from the increase in the number of adrenal medullary tumours diagnosed during the past three years. Of cases of hypertension it appears that a certain percentage owe their symptoms to the release of adrenaline or, more usually, to the non-methylated substance *nor*adrenaline, from an abnormal adrenal gland in which the medullary tissue is greatly hypertrophied. These patients suffer from intermittent attacks of high blood pressure, but there appear to be a few in whom the pressure is also raised above the normal between the attacks (Green, 1946). The diagnosis of the presence of such a tumour is a matter of importance, since its removal is followed by a disappearance of the symptoms.

Tumours examined (Holton, 1949; Swan, 1951) usually contain excessive amounts of active material. The normal suprarenal gland in man, obtained *post mortem*, was found by West, Shepherd, and Hunter (1951) in 36 cases to contain an average of 0.2 mg. of total pressor amine per gramme. This figure may be low, as in laboratory animals it is about 1 mg./g. Tumours have been found to contain from 2 to 20 mg. of total pressor amine per gramme, and this mostly *nor*adrenaline. It is not surprising that the release of some active material causes a rise of blood pressure, and theoretically it should be possible to demonstrate active material in the blood. This is, however, not easy, and Engel and Euler (1950) showed that a large amount of *nor*adrenaline can be found in urine.

Holtz, Credner, and Kroneberg (1947) were the first workers to show that human urine contained adrenaline, *nor*adrenaline, and hydroxytyramine. This last substance

is relatively of low pressor activity. They found from 100 to 150 μg. of adrenaline or *nor*adrenaline, and 2 to 3 mg. of hydroxytyramine per 24 hours. They also stated, without giving figures, that urine from a subject with essential hypertension contained a larger amount of pressor substances than urine from a normal subject.

Euler and Hellner (1951) studied 24-hour urine specimens from 20 young normal subjects. They obtained mean values of 11 μg. of adrenaline and 29 μg. of *nor*adrenaline per subject. They did not find sufficient hydroxytyramine in the extracts to interfere with the estimations.

In the present work the urinary output of pressor substances as obtained by Euler's method of extraction has been investigated. No attempt has been made to divide the pressor activity into adrenaline and *nor*adrenaline; it has been estimated as though it were all *nor*adrenaline.

Method

Extraction of Urine.—The urine was collected into a Winchester bottle containing 5 ml. of concentrated hydrochloric acid. It was stored in the refrigerator at about *p*H 3 whenever more than two days elapsed before it could be extracted. The volume was measured.

An aliquot of 300 ml. was adjusted to *p*H 1–2, and boiled under a reflux for 20 minutes. The acidity was checked during the boiling, as the solution tended to become alkaline. The hot urine was cooled in running water and 4 ml. of 20% (w/v) aluminium sulphate per 100 ml. was added. A smaller amount of aluminium sulphate solution very often failed to produce much precipitate, especially in concentrated urine. The cold urine was first neutralized with 20% (w/v) caustic soda, till the first appearance of aluminium hydroxide; and then the neutralization was completed with 2% caustic soda to *p*H 7.5, using phenol red as an external indicator. The solution was allowed to stand for 10 minutes, when the reaction was readjusted to *p*H 7.5.

The precipitate of aluminium hydroxide was separated by centrifuging at 800 g. for 5 to 10 minutes. The supernatant fluid was decanted off and the precipitate dissolved in 5N sulphuric acid. This solution was carefully neutralized with 20% caustic soda with vigorous mixing, till aluminium hydroxide just failed to be precipitated again; bromphenol blue, as an external indicator, became a greenish colour. This neutralization was important, because an acid solution depressed the blood pressure of the cat used for the final test.

A mixture of one volume of acetone and one volume of alcohol was then added and the solution allowed to stand in the refrigerator for one hour or more, usually overnight. The precipitate and crystals were filtered off and the filtrate was evaporated *in vacuo* to a small volume. This volume, together with the washings from the flask in which evaporation occurred, was 2–4 ml.

Biological Assay.—The extract was compared with a known solution of *nor*adrenaline by intravenous injection into a cat anaesthetized with chloralose and given atropine to exclude vagal reflexes. The amount of the extract which caused the same rise of blood pressure as a given dose of *nor*adrenaline was determined.

Results

Recovery of Added Noradrenaline.—To test the efficiency of the extraction process a specimen of urine was divided into two parts. To one part was added a quantity—for example, 100 μg.—of *nor*adrenaline. Both parts were then extracted, and the difference between the two assays gave the amount of *nor*adrenaline recovered. In 20 observations the mean amount recovered was 100%, the values lying between 75 and 125%. As a further indication of the accuracy of the method, from one specimen of urine two aliquots of 300 ml. were extracted, and both extracts were assayed three times. The figures obtained for the first extract were 29, 34, and 33 μg., and those for the second extract 27, 29, and 29 μg. Other pressor substances may be present in urine. These are piperidine (Euler, 1944), *iso*amylamine (Bain, 1914), tyramine (Bain, 1910), nicotine (Corcoran *et al.*, 1939), and the posterior pituitary hormone (Burn and Singh Grewal, 1951). A series of experiments was carried out in which each of these substances was added in large amount to a sample of urine. The urine was then extracted and tested. It was found that none of them appeared in the extract in sufficient quantity to be mistaken for *nor*adrenaline.

Variation in Daily Excretion.—The excretion of *nor*adrenaline was followed in one subject aged 31 for 14 successive days. The excretion per 24 hours varied from 16 to 86 μg. on different days, which is about fivefold. The mean figure was 41 μg.

Influence of Age.—Urine from older people was found to contain a larger amount of *nor*adrenaline. Table I contains the results on 38 subjects, divided into four age groups. The mean excretion of children, aged from 3 months to 10 years, was 18 μg. of *nor*adrenaline. The mean excretion in the second group, young adults aged from 23 to 30, was 59 μg. of *nor*adrenaline. The difference between these two age groups is significant ($P=0.05$). The mean excretion in the two older groups aged 31–40 and 41–63 was 64 μg. and 71 μg. respectively. These figures are only slightly larger than the figure for the second group, but they conceal the wide variation observed. In adults of any age, the 24-hour excretion of *nor*adrenaline may be at any value from 15 to 150 μg.

TABLE I.—*Influence of Age on the Urinary Excretion of Pressor Amines Estimated as Noradrenaline. The Figures Were Obtained After Hydrolysis of the Urine*

Age Limits	Mean Age	No. of Subjects	Mean *Nor*adrenaline (μg.)
3 months–10 years ..	6	9	18
23–30 years	27	12	59
31–40 ,, ...	32	10	64
41–63 ,, ...	50	7	71

Free and Conjugated Noradrenaline.—Boiling the urine for 20 minutes at *p*H 1–2 hydrolysed any conjugated *nor*adrenaline and rendered it free for adsorption on the aluminium hydroxide. If this preliminary hydrolysis was omitted some so-called "free" *nor*adrenaline was extracted. The results in 12 adults and 9 children are shown in Table II.

TABLE II.—*Mean Excretion of Free and Conjugated Noradrenaline in μg., by Night and by Day, for 12 Adults and for 9 Children. Night for adults was from bedtime to the time of rising. Day for adults was all the rest of the 24 hours. For the children, night was 6 p.m. to 6 a.m., the day 6 a.m. to 6 p.m.*

	Night			Day			Total		
	Free	Conj.	Total	Free	Conj.	Total	Free	Conj.	Total
12 adults	6	17	23	36	28	64	42	43	85
9 children	4	4	8	6	4	10	10	8	18

Conjugated *nor*adrenaline was obtained by subtracting the figure for "free" from that for "total" *nor*adrenaline, which was the result obtained after boiling the urine.

Essential Hypertension.—It is well known that older people commonly have a higher blood pressure than younger people, and one cause of this may be diminished destruction of pressor amines in the blood. Such a diminished destruction might result in increased excretion in the urine. The output of pressor amines was therefore determined in a series of subjects with a blood pressure less than 130 mm., and was compared with the output in a second series having

TABLE III.—*Relation of Excretion of Pressor Amines to Blood Pressure in the Middle-aged*

Normal Blood Pressures				Raised Blood Pressures			
Sex	Age	B.P. (mm. Hg)	*Nor*adrenaline (μg.)	Sex	Age	B.P. (mm. Hg)	*Nor*adrenaline (μg.)
M	52	95	90	M	55	135	150
M	50	115	85	F	50	140	70
F	45	120	60	M	59	155	120
M	48	120	150	F	35	170	67
M	45	120	83	F	57	180	94
M	46	122	69	F	63	190	61
F	63	130	22	F	57	200	36
				F	55	220	46
Mean	50	116	71		54	170	80

a blood pressure greater than 130 mm. The results are shown in Table III. The systolic blood pressures in the first group ranged from 95 to 130 mm., the mean being 116 mm.; those in the second group ranged from 135 to 220 mm., the mean being 170 mm. The ages in the two groups were similar, the means being 50 and 54 respectively. The mean output of pressor amines in the first group was 71 μg. per day and in the second group 80 μg. per day. Thus the subjects with the higher blood pressures did not excrete more pressor amine in the urine than the others.

Toxaemia of Pregnancy.—The excretion of *nor*adrenaline was studied in cases of toxaemia of pregnancy associated with hypertension. The results are given in Table IV. A 24-hour collection of urine was made as soon as possible after the diagnosis, as rest in bed often caused the blood pressure to fall. The normal pregnancy group shown in the table were also resting in bed. Table IV shows that

TABLE IV.—*Relation of Excretion of Pressor Amines to Blood Pressure in Toxaemia of Pregnancy*

Normal Pregnancy			Toxaemia of Pregnancy		
Age	B.P. (mm. Hg)	*Nor*adrenaline (μg.)	Age	B.P. (mm. Hg)	*Nor*adrenaline (μg.)
28	100	26	31	130	38
34	100	57	32	130	46
31	100	63			
23	100	80	31	130	55
36	105	42	24	140	67
30	115	54	29	150	90
29	125	71	29	170	50
Mean: 30	106	56	29	142	58

there was no difference between the two groups, but the blood pressures of those with toxaemias were not very high.

Phaeochromocytoma.—In this series there were three cases of phaeochromocytoma, all suffering from paroxysmal hypertension. At operation an adrenal tumour was removed from each. Table V contains the figures for free and total *nor*adrenaline. It is seen that the figures for *nor*adrenaline are all greater than the highest normal figure, which is about 100 μg. for free *nor*adrenaline and 150 μg. for total *nor*adrenaline. In Case 2 of Table V the tumour itself was examined and found to contain 15 mg. of pressor amines per gramme, of which *nor*adrenaline was about 50% and adrenaline 50%. In addition there were 10 cases of suspected phaeochromocytoma, some of whom were suffering from sustained hypertension and some from paroxysmal hypertension, and whose general symptoms and signs were consistent with the diagnosis. The output of *nor*adrenaline

TABLE V.—*The 24-hour Output of Pressor Amines in Three Cases of Phaeochromocytoma*

Case	Sex	Age	*Nor*adrenaline Output in 24 Hours (μg.)	
			Free	Total
1	F	32	180	180
2	F	33	—	300
3	F	23	2,700	3,800

in these 10 cases ranged from 20 to 100 μg., all being less than the highest normal figure of 150 μg. No case has been operated on, but one patient died, and at the post-mortem examination the adrenal glands were found to be normal.

Discussion

The value of a determination of pressor amines in the urine seems to be confined to the diagnosis of phaeochromocytoma. Euler (1952) has stated that *nor*adrenaline is excreted in increased amounts in a certain proportion of cases of hypertensive disease. Out of a total of 500 cases of hypertension he found that the excretion of pressor amines was normal in about 60% of the cases, but that it was increased in the remaining 40%. He has not yet published details to show the extent of the increase. It is difficult to compare this result with the present work, because the excretion of *nor*adrenaline has been found to increase with advancing years.

The figures for the excretion in the three cases of phaeochromocytoma show a wide variation, and the lowest figure is not very much greater than the highest figure obtained for normal adults. It is reasonably certain that the excretion in patients who have these tumours will depend on the number of paroxysms which they suffer. On a quiet day with no paroxysms the excretion may be low. For certainty of diagnosis it is therefore important that the urine be examined for a period in which paroxysms have occurred.

Urine should not be collected on a day when a benzodioxane test has been carried out. In one case when this was done the benzodioxane test was negative, the systolic pressure rising from 200 to 260 mm. Hg, and the output of pressor amines in the 24-hour period was 490 μg. An abnormally high output of pressor amines was not obtained in this case on three later days.

Green (1946) introduced a source of ambiguity when he showed that 37 out of 53 cases of phaeochromocytoma suffered from sustained hypertension. He defined sustained hypertension by the statement that the blood pressure did not fall between attacks to below 140 mm. systolic and 90 mm. diastolic, or that it did not fall below 95 mm. diastolic. He did not mean that the blood pressure was always at a constant high level.

On present evidence, however, the sustained hypertension of phaeochromocytoma should be marked by a high urinary excretion of pressor amines, while essential hypertension which is accompanied by paroxysms should not.

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REFERENCES

Bain, W. (1910). *Lancet*, **1**, 1190.
—— (1914). *Quart. J. exp. Physiol.*, **8**, 229.
Burn, G. P., and Singh Grewal, R. (1951). *Brit. J. Pharmacol.*, **6**, 471.
Corcoran, A. C., Helmer, O. M., and Page, I. H. (1939). *J. biol. Chem.*, **129**, 89.
Engel, A., and Euler, U. S. von (1950). *Lancet*, **2**, 387.
Euler, U. S. von (1944). *Acta physiol. scand.*, **8**, 380.
—— (1952). *II Congrès International de Biochimie, Symposium sur les Hormones Protéiques et Dérivées des Proteines*, p. 39. Sedes, Paris.
—— and Hellner, S. (1951). *Acta physiol. scand.*, **22**, 161.
Green, D. M. (1946). *J. Amer. med. Ass.*, **131**, 1260.
Holton, P. (1949). *J. Physiol.*, **108**, 525.
Holtz, P., Credner, K., and Kroneberg, G. (1947). *Arch. exp. Path. Pharmak.*, **204**, 228.
Swan, H. J. C. (1951). *British Medical Journal*, **1**, 440.
West, G. B., Shepherd, D. M., and Hunter, R. B. (1951). *Lancet*, **2**, 966.

The Turkish National Bibliographical Institute has started publication of a monthly selective bibliography of articles appearing in Turkish periodicals. Information is given in Turkish and French, classification is by the International Decimal Code, and there is an index of authors and journals which will be cumulated annually. Medicine is well represented in the bibliography, which may be obtained from Milli Kütüphane, Ankara.

CROHN'S DISEASE INVOLVING THE STOMACH

A REPORT ON TWO CASES

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Crohn's disease is now a well-recognized pathological and clinical entity. It is generally agreed that the characteristic lesions occur predominantly in the terminal ileum, but that "skip" lesions are found anywhere in the jejunum, ileum, or colon. Crohn (1949) describes three main varieties: regional ileitis, ileo-jejunitis, and ileo-colitis. He also mentions cases in which the second and third parts of the duodenum were involved, and states that in two of these there were radiological appearances suggesting spread of the disease to the stomach. So far as we are aware, no cases have been published in which there has been proof of the disease occurring in the stomach, nor have the clinical or radiological features been described. In the following two cases Crohn's disease was shown to be present in the stomach.

Case 1

A single woman aged 23 was first seen on May 6, 1949, when she complained of peri-umbilical pain, accompanied by vomiting. Her vomit was alleged to have contained streaks of blood. Her appetite was good, she had no indigestion, and her bowels were said to act normally. Examination revealed the presence of a small, tender, irreducible umbilical hernia, which was dealt with by operation. She returned to the out-patient clinic one year later complaining of repeated attacks of epigastric pain, lasting for one to two hours at a time, associated with nausea. She had not lost any weight and had had no diarrhoea. Nothing abnormal was found on examination except some generalized abdominal tenderness. The operation scar was soundly healed.

During the next three months she was kept under observation, and a series of barium meals at six-weekly intervals revealed changes which may be summarized as follows. (*a*) There was absence of normal peristalsis in the pyloric antrum and cap. (*b*) There was deficient mucosal pattern in the pyloric antrum, the duodenal cap, and the upper half of the second part of the duodenum. The transition from normal to pathological mucosa was sharp and well defined in the stomach (Fig. 1) and in the second part of the duodenum (Fig. 2). Above and below the involved area the mucosal relief pattern was normal. Throughout the affected region the margins of the barium-filled lumen were slightly irregular, suggesting the possibility of superficial ulceration, but no definite ulcer crater was identified. The duodenal cap showed some contraction of the fornices, and its mucosa was devoid of folds. In the second part of the duodenum the usual feathery pattern was replaced by an unbroken column of barium until the normal mucosa was reached. The whole of the involved area remained motionless, showing complete absence of peristalsis, and even the cap was persistently full of barium. (*c*) There was no gastric or small-bowel stasis, and the colon showed no gross abnormality. At the *x*-ray examination on August 8, 1950, early changes in the mucosal pattern of the last 2 in. (5 cm.) of the terminal ileum were detected for the first time. (*d*) Her lung fields were normal, except for a calcified focus.

The changes in the stomach and duodenum were interpreted as a gastroduodenitis, and, in view of the appearances of the terminal ileum, a provisional diagnosis of Crohn's disease associated with a gastroduodenitis was made.

During the three months she was under observation as an out-patient her general condition steadily deteriorated. On August 20 she was admitted to hospital. By this time her vomiting had become more insistent and she could retain only water. Attacks of severe abdominal pain occurred, but she had no diarrhoea during the week she was in bed before operation. Her pulse rate varied considerably, rising at times to 120–130, and she had some pyrexia. Though on palpation generalized abdominal tenderness persisted, at no time was there any distension or rigidity of the abdomen. Her haemoglobin was 82% and her E.S.R. (Westergren) was 38 mm. in one hour.

FIG. 1.—Case 1. Showing the absence of mucosal folds in the antrum, cap, and upper half of the descending part of the duodenum. The arrows indicate the junction of the normal and pathological mucosa.

On August 29 it was decided to explore her abdomen. Typical changes of Crohn's disease were found in the terminal ileum and irregular inflamed patches were present throughout the colon. The stomach wall appeared to be only a little thickened, but in view of the previous barium-meal reports a biopsy of the gastric mucosa was taken from the region of the pyloric antrum. The disease was clearly too widespread for any benefit to be expected from short-circuiting or excision of affected portions of the bowel. The abdomen was therefore closed.

FIG. 2.—Case 1. Showing the irregular margins of the duodenal cap and absence of folds in the mucosa of the cap and upper descending duodenum.

The histological report on the gastric biopsy was: "The stroma is heavily infiltrated by lymphocytes, plasma cells, and endothelial cells. Giant cells are present. No caseation or tubercle bacilli were found. A chronic granulomatous process like Crohn's disease appears to be present."

After operation the patient appeared to convalesce satisfactorily. In view of her pyrexia it was decided to try the effect of a course of streptomycin, which was given with apparent benefit. Her vomiting became much less frequent, and she was sent home on the sixteenth day.

Her subsequent history is of interest. Some weeks after going home persistent vomiting and anorexia returned. She became seriously ill. Though she remained at home, in retrospect it is clear that she should have been readmitted to hospital at this time, since the difficulties of giving her enough nourishment might then have been decreased. As it was, she started to make a slow improvement in the spring of 1951, and was well enough to come to the follow-up clinic in August. She then stated that there had been much less vomiting and abdominal pain in recent months, and that she was feeling much better. A barium meal was given on September 10. It showed that active peristalsis had now returned to the pyloric region and to the whole of the duodenum. Though there was still some residual narrowing of the lumen of the antrum, the outline was smooth and the mucosal relief pattern was normal. There was, however, delay in the emptying of the ileum, where after seven hours a considerable residue of barium remained. The last 3 in. (7.6 cm.) of the terminal ileum showed narrowing, and there was a typical Steirlin sign in the caecum. The ileum proximal to the narrowed portion was slightly dilated (Fig. 3). The *x*-ray appearances had therefore, after 12 months, become those typically found in regional ileitis.

FIG. 3.—Case 1. Showing the typical appearances of Crohn's disease in the terminal ileum and caecum at the end of the first year.

FIG. 4.—Case 2. One year later, when peristalsis and mucosal pattern were absent from antrum, cap, and upper descending duodenum.

Case 2

A married woman aged 24 with two children was first seen in June, 1950. She complained that during the past three years she had suffered from lack of energy, lassitude, and attacks of abdominal pain and diarrhoea. Her stools were watery, but did not contain blood or mucus; her pain was relieved by evacuation of the bowels. Her appetite was good. On examination the only abnormal finding was tenderness in the right iliac fossa, where there seemed to be a palpable swelling. She was admitted to hospital for observation. The results of investigations were as follows: F.T.M. was normal, haemoglobin 73%, and no pathogenic bacteria were found in her stools. On October 30 a barium meal showed normal functioning of the stomach and duodenum. No gross changes were seen in the small bowel.

She returned home, and on a subsequent visit complained of a vaginal discharge, for the treatment of which she was referred to a gynaecologist. He detected the presence of an ovarian cyst, and on February 7, 1951, he performed a laparotomy. The cyst was removed. On examination of the small bowel it was obvious that the terminal ileum was affected by changes indicating the presence of Crohn's disease. She was then referred to one of us (F. R. R. M.), and on April 6, when the abdomen was reopened, the diagnosis was confirmed. As the disease appeared to be confined to the terminal ileum, a right hemicolectomy was carried out, the caecum, ascending colon, and the last 3 feet (0.9 metre) of the ileum being resected. Histological report on the excised bowel confirmed the diagnosis.

She made a good recovery from the operation. When seen as an out-patient two months later she still complained of frequent motions, but the abdominal pain had disappeared. On August 21 she complained of anorexia and repeated vomiting. She had lost 14 lb. (6.4 kg.) in weight since her previous visit, and looseness of the bowels still continued to trouble her. She looked ill, but examination of her abdomen failed to reveal any significant abnormality. Further investigation showed that her E.S.R. had risen from 12 to 23 mm. in one hour. Her haemoglobin was 80%. The clinical picture thus seemed similar to that found in Case 1, and this opinion was confirmed when the supporting evidence of a barium meal was obtained (R. J. C.). The report may be summarized as follows: (1) There was pronounced gastric dilatation, with an excess of fasting juice. (2) Gastric peristalsis was almost completely absent. (3) The normal mucosal pattern in the pyloric antrum and in the duodenal cap was absent (Fig. 4). (4) The emptying rate of the stomach was normal. In six hours all the barium was in the colon, and in 24 hours most of it had reached the sigmoid.

Comparison of films taken at this time with those taken on October 30, 1950, showed that a great change had occurred in the interval. It was now clear that the change in symptoms had a pathological basis—that is, that of a gastroduodenitis, the nature of which might well be presumed to be similar to that described in Case 1.

Her subsequent history has amply confirmed this opinion. She has been in hospital since October, 1951. Her general condition has deteriorated on account of persistent anorexia and vomiting, and consequent inability to take adequate nourishment. She has become anaemic (Hb 63%) and suffers from frequent pyrexia. Oedema from alteration in serum proteins has occurred, and at times since admission to hospital it has often seemed as if she were going to die.

Discussion

These two cases appear to shed fresh light on the significance of anorexia and vomiting in cases of Crohn's disease. It would seem that such symptoms may herald the onset of this disease, and that when Crohn stated that "nausea and vomiting are rare manifestations and only occur in the later stenotic phases of the disease. Appetite is usually well preserved," he had not this possibility in mind. In neither of the above two cases was stenosis a primary feature. In fact, it was found only in the later stages of Case 1 when vomiting had ceased to feature in her complaints and when her gastric symptoms had largely subsided. No stenotic lesion was demonstrated in Case 2. It therefore seems justifiable to assert that when persistent anorexia and vomiting occur in Crohn's disease, and if other clinical evidence of intestinal obstruction is absent, the possibility of the stomach and duodenum being involved in the pathological process should always be considered. Having seen two cases of gastroduodenitis due to Crohn's disease in the limited practice of one surgeon in the last 18 months, we

feel that it is important to examine the stomach and duodenum carefully when clinical features such as we have described are encountered, since it may well be that these cases are less rare than a reading of the literature would suggest, and that this aspect of Crohn's disease has not received adequate attention.

The *x*-ray changes we have described are in our opinion characteristic. Further comment on the radiological findings may be made as follows: First, had the changes in Case 1 been confined to the stomach they might have been attributed to cancer of the diffusely infiltrating type (linitis plastica), but associated involvement of the duodenum and consideration of the age of the patient were of value in leading to a correct diagnosis. Secondly, the follow-up *x*-ray films of this case are also of interest in showing that the changes in the mucous membrane of the stomach and duodenum are not necessarily of a permanent nature, and that with the passage of time a return to a normal mucosal pattern is possible.

It should also be noted that both these patients became very ill on account of inability to assimilate adequate quantities of food. Case 2, which we have been able to observe in hospital, showed an upset in the protein content of the blood, and we feel it is important to stress the need for adequate dietetic care. Both these patients became anaemic, both appeared at one time to be going to die. A high-protein diet, as well as the prescribing of iron and vitamins, appears to us to be of importance in the handling of these cases.

Summary

Two cases of Crohn's disease involving the stomach and duodenum are reported; one of them was confirmed by biopsy of the gastric mucosa.

The radiological changes are described in detail.

We would like to thank Dr. H. S. Kellett for the pathological report and Mr. P. Harrison for the photographs.

REFERENCE

Crohn, Burrill B. (1949). *Regional Ileitis*. Staples Press Ltd., London.

TOXOPLASMOSIS IN RELATION TO MENTAL DEFICIENCY

BY

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Mental deficiency is a social problem and does not constitute a clinical or pathological entity. On the contrary, it indicates a degree of mental retardation ranging from the near normal to a completely vegetative state. It is even less of a disease entity than is, for example, jaundice, and, like jaundice, it may be produced by a very large number of noxious agents.

The severer degrees of mental deficiency—that is, idiocy and imbecility—are now recognized to be always attended by cerebral lesions, often gross and obvious. The causes of these lesions are, however, far from obvious. The diagnosis of "primary amentia" is often made, though, as in other fields of medicine, the use of the word "primary" is a cloak for our ignorance of the aetiology.

In the absence of any specific medical treatment for mental deficiency interest in this field of medicine is naturally concentrated on prevention, for which a knowledge of aetiology is essential. It is understandable, therefore, that whenever any new suggestion is made regarding the cause of even a few cases of mental deficiency it should be eagerly grasped at and explored by those working in this branch of medicine.

Toxoplasmosis as a cause of mental deficiency has been considered in America and on the continent of Europe. Accounts of the cerebral pathology are given by Wolf, Cowen, and Paige (1939) and by Gard *et al.* (1949). The clinical and pathological pictures vary considerably, but the introduction of reliable skin and serological tests has raised hopes of a more precise diagnosis.

The skin and serological tests were recently carried out by Dr. O. D. Fisher at the clinical laboratory of the Hospital for Sick Children, Great Ormond Street, on the entire population of a group of institutions for certified mental defectives, comprising 698 patients, made up of 623 children almost equally divided between the sexes, and 75 adult females. Details of the technical aspects of the testing, together with the results of the survey, were reported by Fisher (1951). As the present paper is complementary to Fisher's survey his findings are briefly summarized as follows:

All the patients were skin-tested, and those of the children who proved to be skin-positive to toxoplasmin had samples of venous blood examined serologically, using Sabin and Feldman's dye or cytoplasm modifying test. An excellent correspondence between the skin test and the serological reaction was obtained. Of the 698 patients tested, 55 showed dermal sensitivity to toxoplasmin (T-positive). Of these, 20 were female adults who did not have their serum tested. The remaining 35, who were children, were positive to the dye test. Of the skin positive children, 14 were boys and 21 girls. Twenty serological tests done on toxoplasmin-skin-test-negative patients were all negative. In 14 T-positive cases lumbar puncture was carried out. In none of these did the cerebrospinal fluid show any abnormality, and toxoplasmas were not found.

Present Investigation

In this investigation a note has been made of the percentage incidence of positive reactors in the different age groups of the 698 patients tested in Fisher's survey, and the 55 patients who showed positive toxoplasmin skin and dye reactions have been scrutinized clinically and radiologically for signs of toxoplasmosis.

Methods of Examination.—The scrutiny consisted in physical and ophthalmic examination and radiography of the skull. As a guide in the examination we used the criteria cited by Sabin (1948)—internal hydrocephalus or microcephaly; chorioretinitis with predilection for the macular region; convulsions and other signs of involvement of the nervous system; and cerebral calcification.

Results

Incidence of Positive Reactions.—The age distribution of patients who were positive is shown in Table I. These figures show a steady and significant rise in the proportion of positive reactions with age.

Physical Findings.—As all the patients examined were mentally defective it was to be expected that they would

TABLE I.—*Incidence of Positive Toxoplasmin Reactions in Different Age Groups of 698 Mental Defectives*

Ages:	0–4	5–9	10–14	15–19	20–24	25–29	30–39	40–49	50–60	Total
Total	65	246	192	108	29	16	13	17	12	698
Pos.	0	9	13	10	5	3	3	5	7	55
% Pos.	0	3·6	6·7	9·2	17·2	18·7	23·0	29·4	58·3	7·9

show certain non-specific physical abnormalities such as are commonly associated with the severer forms of mental defect—for example, dwarfing of stature, appearance of extreme youth, vascular stasis at the extremities. Moreover, many of the T-positive patients had been admitted to hospital with a recognized syndrome or obvious physical anomaly, and these would naturally show appropriate signs. The designation of the T-positive cases is shown in Table II.

TABLE II.—*Abnormalities Observed in Toxoplasmin-positive Cases*

Epilepsy	13	Microcephaly	1	Strabismus	5
Cerebral palsy and spastic diplegia	2	Epiloia	1	Deafness	3
Hemiplegia	5	Phenylketonuria	1	Psychotic features	2
Chorea	1	Hydrocephalus	1	Pleural effusion	1
Mongolism	2	Hypertelorism	1	Kyphoscoliosis	1
		Nystagmus	4	Psoriasis	1

Familial mental defect was noted in seven cases, and one case was the product of incest.

In carrying out the physical examination many abnormalities of this kind were found, but there was no frequently recurring pattern of physical signs to suggest that the cases had been subjected to the same pathogenic agent.

Degree of Mental Defect.—The distribution on the basis of intelligence tests of the T-positive cases is shown in Table III. The intelligence of T-positive patients varied

TABLE III.—*Degree of Mental Defect Observed in the 55 Toxoplasmin-positive Patients*

I.Q.	Classification	No.	%
0–20	Idiots	18	33
20–50	Imbeciles	27	49
50–70	Feebleminded and educationally subnormal	4	7
70+	Within normal range	6	11

within wide limits from a vegetative idiot with an estimated "social quotient" of 2 up to a neurotic girl with an intelligence quotient of 104. The sample is overweighted with high-grade imbeciles by the fact that the older patients in the Fountain group are for administrative reasons mainly of that level.

Ophthalmological Findings.—The eyes of all the patients were examined. In 50 cases the examination included ophthalmoscopy. The results are shown in Table IV. Findings similar to those regarded by Binkhorst (1948) as suggestive of toxoplasmosis were encountered in the eyes of only two patients. In one case there was a macular scar with calcareous dots in the right eye, and an associated temporal pallor of the disk; the left eye was normal. In the second case the appearances were less definite: in addition to a few dots scattered over both fundi, one fundus showed a reticular reaction temporal to the macula.

TABLE IV.—*Ocular Anomalies Observed in 55 Toxoplasmin-positive Cases*

Cataract	2	Macular lesion with choroidal sclerosis	1
Microphthalmos	5	One eye absent	2
Corneal opacity	1		
Optic atrophy	1		

Radiological Findings.—Routine *x*-ray examination of the skulls of positive cases did not show any calcification which could be regarded as pathognomonic. In one instance, a case of tuberose sclerosis, there was an appearance consistent with calcification of the glial nodules which is sometimes encountered in this condition. Four patients showed calcification of the pineal body. One patient had a cluster of opacities compatible with calcification in the choroid plexus of the lateral ventricle, another showed a small fleck of calcification in the temporal region, whilst in another there was a calcification of the falx cerebri. The only other case of radiological interest showed a striking and unusual picture of large plaques of calcification extending into the meninges within a hydrocephalic skull, particularly along the falx cerebri. This patient's deficiency was attributed by the parents to a fall down 20 steps at the age of 2. The radiological picture was compatible with calcification in an old subdural haematoma.

Discussion

The present findings show that positive skin and dye tests for toxoplasmosis are not uncommon in a population of mental defectives. However, this occurrence does not seem to be any more common in such patients than in the general population (Fisher, 1951). The incidence of positive reactions rises with increasing age in a like manner to other immune reactions—for example, the Schick test (Zingher, 1923, 1924). From this, and the absence in the clinical record of the positive patients of any illness which could be attributed to toxoplasmosis, it is suggested that the immune reaction is incidental.

In almost all our cases the mental deficiency was produced by factors operating before, at, or immediately after birth. But the figures presented suggest that the toxoplasmin-positive reaction is usually acquired some years after birth. It follows from this that toxoplasmosis is unlikely to be a frequent cause of mental deficiency.

It is known that some causes of gross brain damage operate only very infrequently. Thus in the population of the Fountain group at the present time (approximately 700) there are no cases definitely diagnosed as cerebromacular degeneration, Tay–Sachs's disease, or Schilder's disease, and only two with a diagnosis of gargoylism and one due to tuberculous meningitis. It may therefore be that, despite the negative conclusions drawn from the present investigation, toxoplasma does occasionally pass the placental barrier to produce a degree of brain dramage compatible with survival of the infant.

It is clear that Binkhorst's assumption that positive serology confirms that abnormalities found in the patient—for example, hydrocephalus or microcephaly—are necessarily due to toxoplasmosis cannot be supported.

The results of the present survey do not permit any conclusions to be drawn on the possible incidence of a more acute form of toxoplasmosis which might prove fatal before admission to an institution for mental defect could be secured. A survey of toxoplasmin sensitivity in the mentally defective and the normal infant under 1 year might be helpful.

As to the origin of the positive reactions, if one assumes that the tests correlate with infection with actual toxoplasma there is no difficulty in explaining the exposure. Of the patients who have stayed in an institution for long periods of time, most have lived at home for varying periods, usually of several years. In that time they have had contact with cats and dogs, even though drawn from an urban area (principally that of the County of London in the case of our patients). Whilst in hospital contact with cats is common, since each ward has one or more cats. Two wards have canaries. A small "zoo" is kept within the hospital grounds. Despite all the efforts of the staff, periodic invasions of vermin—rats, mice, and beetles—occur. Furthermore, the ubiquitous sparrow leaves his droppings in all the playgrounds. Toxoplasma has been shown to live in a tremendous number of hosts, including dogs, rabbits, guinea-pigs, mice, rats, monkeys, pigeons, English sparrows, starlings, canaries, swallows, thrushes, chaffinches, and linnets. Also the organism has been found pathogenic for the cat, the pig, the shrew, the domestic hen (Wolf, Cowen, and Paige, 1939), and the hare in Denmark (Christiansen and Siim, 1951). Clearly the possibility of infection is widespread, but there is as yet little evidence to suggest that risk is worthy of special measures for its avoidance.

At different times the thesis has been advanced that mental defectives differ from the rest of the population in response to disease. In view of the gross cerebral pathology in idiots this might be thought likely, but there is no concrete evidence that immunological reactions are in fact different. On the contrary, the experience of this hospital in regard to the Schick test shows a normal response, as does the Mantoux reaction (Kirman, 1951). There is nothing in the present set of figures to suggest an abnormal response pattern to toxoplasmin in our hospital population.

Summary

The 55 toxoplasmin-positive patients found in a population of 698 mental defectives have been scrutinized for evidence of toxoplasmosis. Most of the patients were children. The incidence of positive cases increased with advancing age. In two cases eye lesions suggestive of toxoplasmosis were found. Radiology and lumbar puncture showed no findings suggestive of toxoplasmosis. In no cases could the mental defect be definitely attributed to toxoplasmosis. In some cases other definite causal factors were present—for example, epiloia, phenylketonuria, mongolism. It was concluded that in mental institutions or elsewhere a positive toxoplasmin reaction is acquired like a positive Schick reaction with increasing age, and is very infrequently associated with clinical toxoplasmosis; and that toxoplasmosis is not a common cause of mental defect.

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REFERENCES

Binkhorst, C. D. (1948). *Toxoplasmosis*, p. 128. Leyden.
Christiansen, M., and Siim, J. C. (1951). *Lancet*, 1, 1201.
Fisher, O. D. (1951). Ibid., 2, 904.
Gard, S., Magnusson, J. H., Wahlgren, F., and Gille, G. (1949). *Pediatrics*, 4, 432.
Kirman, B. H. (1951). *J. ment. Sci.*, 97, 783.
Sabin, A. B. (1948). In Brennemann's *Practice of Paediatrics*, 4, 46. Hagerstown.
Wolf, A., Cowen, D., and Paige, B. H. (1939). *Amer. J. Path.*, 15, 657.
Zingher, A. (1923). *Amer. J. Dis. Child.* 25, 392.
—— (1924). *Amer. J. publ. Hlth.* 14, 955.

MYXOEDEMA AS A CAUSE OF DEATH

REPORT OF TWO CASES

BY

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Since the introduction of treatment with thyroid extract by Murray in 1891, it has been presumed that myxoedema as a cause of death is rare. We have been able to find only three recent references, and therefore report the following two cases.

Case 1

A woman aged 61 was admitted to hospital on January 7, 1951, with the following history. Thirty-five years ago she developed a left-sided hemiplegia, from which she made a good recovery. Two years ago she had another stroke, also involving the left side. Again recovery was fairly complete. The patient had had four children without trouble and the menopause had occurred at the age of 48. She had been in fairly good health until a fortnight before admission, when a cold and a severe cough developed. Her condition gradually deteriorated until January 6, when she first called in her doctor. He found her semi-conscious, and the following morning noticed considerable puffiness of the face.

On admission her pulse rate was 62 and temperature 97° F. (36.1° C.). She was moderately obese, and had pronounced supraclavicular fat pads. She was extremely lethargic but obeyed simple commands. Her voice was low-pitched and croaking. The scalp hair was dry and scanty, the pubic hair was extremely sparse, and the axillary hair was missing. Her skin felt dry and cold; her face, especially the eyelids, was puffy. Nothing abnormal was found in the heart, lungs, or abdomen. The blood pressure was 140/100 mm. Hg. There was pitting oedema of the legs up to the knees, and the hands were swollen but did not pit on pressure. Some evidence of previous hemiplegia was found in slight spasticity of the left side with an extensor plantar response, but there was no other abnormality in the central nervous system.

Investigations.—Urine: albumin was present; film showed scanty red cells, leucocytes, and mixed bacterial flora. The haemoglobin was 90%; blood urea, 50 mg. per 100 ml.; blood sugar, 57 mg. per 100 ml.; blood cholesterol, 390 mg. per 100 ml.; serum potassium, 18.4 mg. per 100 ml.; serum sodium, 345 mg. per 100 ml.; plasma chlorides, 595 mg. per 100 ml.; serum protein, total 7.2% (albumin 3.7%, globulin 3.5%, A/G ratio 1.1). An electrocardiogram showed flat and inverted T-waves in all leads, suggestive of myxoedema.

The diagnosis was difficult. Renal failure was suspected, but there was no confirmatory evidence on investigation. It was thought that an adrenal failure might be the cause, so treatment was started with penicillin and adrenal cortical extract, 10 ml. four-hourly. Although the patient became brighter mentally, her general condition deteriorated, respiration became laboured, and she died four days later. Her temperature remained at a low level all the time, and varied between 95 and 97° F. (35 and 36.1° C.). Her pulse rate varied between 60 and 70.

Necropsy

The following were the outstanding features: a widespread consolidation of the lungs; ante-mortem haemorrhages involving the suprarenals; remnants of thyroid gland; a heart of normal size and coronary vessels normal for her age.

Histological Examination.—Sections taken from both lobes of the thyroid gland showed marked fibrosis. A few small islets of lymphoid tissue were present in each lobe, and within these the remains of thyroid acini could be identified. The latter were composed of large pale irregular cells showing variable eosinophilic staining properties. Colloid was absent except in one small area. These remaining acini were surrounded by plasma cells and an outer zone of small lymphocytes. The *lungs* showed the picture of grey hepatization, with the alveoli distended by polymorphonuclear exudate. No heart-failure cells were present. *Kidneys:* the cortex was thinner than normal and patchy interstitial fibrosis was present. A considerable number of normal-looking glomeruli were to be seen. The vessels showed some thickening of the walls, but no elastosis.

Evidence of antemortem haemorrhage was found in the *suprarenal gland.* The *pituitary gland* was larger than normal. Acidophilic staining cells were noted to be extremely scanty, otherwise the histological appearance was within normal limits.

Case 2

An unmarried woman aged 50 was admitted to hospital on January 7, 1952. The previous history was that she had been well enough to do her own housework until five months before admission. Since then she had complained of weakness and of feeling cold, and these symptoms had gradually become worse. On the day of admission she suddenly complained of loss of vision, and the doctor found her lying across the bed unconscious.

On admission her temperature was 95° F. (35° C.) and pulse 42. She was semi-conscious and repeated such sentences to herself as, "What have I done?"; but she would obey simple commands. Anasarca was present and the face and eyelids were swollen. The skin was coarse and dry. The scalp, pubic, and axillary hair was scanty; the superciliary hair was absent. Coarse rales were heard at the bases of both lungs, and there was tracheal rattle; the heart sounds were normal; the blood pressure was 250/140 mm. Hg. Nothing abnormal was found in the abdomen or in the central nervous system.

Investigations.—Urine: albumin was present; film showed many Gram-negative bacilli. The blood urea was 25 mg. per 100 ml.; blood cholesterol, 495 mg. per 100 ml.; serum sodium, 295 mg. per 100 ml.; plasma chloride, 420 mg. per 100 ml.; alkali reserve, 44 c.cm. CO_2; serum protein, total 6% (albumin 3.4%, globulin 2.6%, A/G ratio 1.3). The cerebrospinal fluid contained 1 white cell per c.mm. and 56 mg. of protein per 100 ml. An electrocardiogram showed flat T-waves in all leads; the tracings were compatible with the diagnosis of myxoedema.

Ten hours after admission the patient had a tonic fit. She was given a small amount of thiopentone intravenously, when the respiration stopped and the pulse became impalpable. Artificial respiration was started and she recovered. She was treated with continuous oxygen and penicillin, 1,000,000 units six-hourly. She improved considerably, but remained confused and slightly maniacal. Her blood pressure was about 160/100 mm. Hg. On January 10 she was given 10 mg. of thyroxine, with great improvement in the general condition. The puffiness and the subcutaneous oedema disappeared and the blood cholesterol fell to 388 mg. per 100 ml. Nine days later her temperature went up to 101° F. (38.3° C.), her breathing became laboured, and her general condition deteriorated. On the 21st day she became unconscious and her pulse impalpable, and she died.

Necropsy

A full post-portem examination revealed very little positive information. Macroscopically the heart and coronary arteries appeared normal.

Histological Examination.—The *thyroid gland* was slightly enlarged and the cut surface firm and pale. The histological appearance was that of a Hashimoto or lymphadenoid goitre. *Kidneys:* Both were of normal size and appearance. Histological examination showed slight thickening and elastosis of the vessels. An occasional glomerulus was undergoing hyalinization. Adequate numbers of normal-looking glomeruli were present, however, and there was no evidence of tubular degeneration or interstitial fibrosis. The appearance was thought to fit in with an early hypertensive kidney.

The *pituitary gland* seemed to be quite normal. The ovaries were fibrotic.

Discussion

In our opinion myxoedema was the main cause of death in both cases. In Case 1 it can be presumed that a patient with severe untreated myxoedema was exposed to the stress of pneumonia and that this produced suprarenal failure. McGavack (1951) says that there is atrophy of the zona fasciculata in myxoedema and the excretion of 17-ketosteroids and glucocorticoids is greatly diminished. It seems feasible that when such a gland is exposed to additional stress acute adrenal cortical failure may ensue. The fact that there was widespread haemorrhagic destruction of the adrenal glands is in agreement with this assumption.

Case 2 is not quite so conclusive. Hypertensive encephalopathy had to be considered in the differential diagnosis. The reasons, however, against hypertension playing a major part in the fatal outcome of this case are: (1) the normal appearance of the eye background; (2) the normal size of the heart; and (3) the electrocardiogram, which was suggestive of myxoedema rather than of hypertension. The fact that the blood pressure, except on admission, was within normal limits is also against this diagnosis.

Recent reports of death due to myxoedema are scanty. The largest series is that by McGavack and Schwimmer (1944), who described nine deaths, all due to cardiac complications of myxoedema. One case was described by Foster and Barr (1944) in which there was myxoedema of long duration with slow deterioration. A case was reported by Chiolero and Meerwein (1939), but it was doubtful whether myxoedema was responsible for death, as the case was complicated by the presence of schizophrenia and chronic ulcerative colitis. The largest series described was in a Report on Myxoedema (1888) in which 22 cases were mentioned. There it was stated that the majority of the patients died from intercurrent diseases, mainly pulmonary or renal, but in some cases death was the direct result of myxoedema. These cases showed intense anaemia and a variety of nervous symptoms, such as maniacal excitement, coma, etc.

A very interesting report has recently been published by Sheehan and Summers (1952) which stressed the important part that hypothermia played as a cause of coma in similar cases. In their patients the rectal temperature was recorded as 77 and 83° F. (25 and 28.3° C.). They point out that the clinical thermometer does not register below 95° F. (35° C.) and therefore this condition goes unrecognized. In retrospect, it is probable that our two cases fall into the same class. The temperature recorded in Case 1 was between 95 and 97° F. (35 and 36.1° C.), which most likely meant that the thermometer did not register, and the difference in the temperature depended only on how far the mercury column was pushed down by the nurse. In Case 2 the temperature was recorded on admission as 95° F. (35° C.). Only after the administration of thyroxine were temperatures above 98° F. (36.7° C.) recorded. The pulse rate in both cases was very low, which is in agreement with the observations recorded by Sheehan and Summers. Perhaps a significant fact is that both cases were admitted in the middle of winter, when the danger of hypothermia is obviously greatest.

The lesson to be learned from our cases is that under certain circumstances myxoedema may be a fatal disease. Therefore it is essential to diagnose these cases early and to treat them promptly. Unfortunately, the possibility of myxoedema may not even be considered. In our cases the diagnosis on admission was chronic nephritis, and that is probably the most common mistake. The patients may also be treated with iron and liver in the belief that the condition is due to anaemia, or cardiac disease may be suspected. It is important to stress the fact that the diagnosis may not only be missed in life but that, even when a necropsy is done, it may remain uncertain because the thyroid gland may not be examined.

In Case 2 the thyroid gland was of normal size, and only on histological section could destruction be confirmed. For these reasons we think that this condition may often remain undiagnosed.

Unfortunately, treatment of these two cases was not successful. In Case 1 adrenal cortical extract was used but did not prevent the fatal outcome. In Case 2 we had the experience of the first to suggest the possible diagnosis. The patient was given an adequate dose of thyroxine without success. Probably, irreversible change had taken place before treatment was begun. The answer is, of course, early diagnosis.

Summary

Two cases in which death was due to myxoedema are reported. It is suggested that this diagnosis is often missed, and that it is necessary to examine the thyroid gland after death as a routine procedure, particularly in elderly people.

Treatment of myxoedema in the last stages is ineffective; therefore it is essential to diagnose and treat it early.

Our thanks are due to Dr. A. J. Hardy, who performed the necropsy on Case 2 and allowed us to be present and gave facilities for histological examinations; to Dr. A. Anderson for help in the interpretation of electrocardiograms; and to the laboratory staff of the Royal Berkshire Hospital, Reading.

REFERENCES

Chiolero, J., and Meerwein, F. (1939). *Schweiz. med. Wschr.*, **20**, 623.
Foster, M., and Barr, D. P. (1944). *J. clin. Endocr.*, **4**, 417.
McGavack, Th. H. (1951). *The Thyroid*, p. 145. London.
—— and Schwimmer, D. (1944). *J. clin. Endocr.*, **4**, 417.
Report on Myxoedema (1888). *Trans. Clin. Soc. Lond.*, **21**, Suppl.
Sheehan, H. L., and Summers, V. K. (1952). *British Medical Journal*, **1**, 1214.

PELVIC EVISCERATION WITH PRIMARY BOWEL AND URETERIC ANASTOMOSES

BY

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The operation of pelvic evisceration, which was conceived and had its early years in the United States of America, has aroused general interest and has now been sporadically practised here. A modification of this operation, on a patient with a carcinoma of the rectosigmoid region invading the bladder, is presented. In one stage the affected portion of the bowel, with the bladder, prostate, and vesicles, was excised, the pelvic colon was anastomosed to the stump of the rectum, and the ureters were transplanted into the colon. This case represents a fusion of the present tendency towards widespread excision of pelvic organs for advanced carcinoma and that of preservation of the anal sphincter where indications are favourable. The satisfactory functional result has prompted an early report, but final assessment must await the years.

Case Report

A married man aged 55 eighteen months before admission to hospital had had an attack of "colitis" which lasted 10 days. Subsequently he had had two normal stools a day until the week preceding his visit, when his stools had increased to four a day. For three weeks he had had dysuria and frequency, and admitted to having passed wind and some solids in his urine.

Examination showed a large sausage-shaped tumour in the line of the descending colon and then curving above the inguinal ligament. An enema reduced this swelling to a small mass in the pelvis, easily palpable bimanually. A barium enema confirmed a blockage in the sigmoid colon. On sigmoidoscopy no rectal abnormality could be found, and no tumour could be reached with the sigmoidoscope at the maximum attainable distance of 8 in. (20 cm.). Microscopical examination of the urine showed a large number of pus cells with 520 mg. of protein per 100 ml., and cultures gave a profuse growth of *Bact. coli*. The blood urea was within normal limits. By intravenous pyelography the kidneys seemed normal, but the bladder shadow was distorted superiorly by an irregular filling defect. Cystoscopy confirmed a fistula in the postero-superior part of the bladder with marked granulation or tumour formation about the opening.

A carcinoma of the sigmoid colon with vesico-colic fistula was diagnosed, and the possibility of having to excise all the pelvic viscera was considered. The bowel was prepared for operation with phthalylsulphathiazole, 2 g. six-hourly for six days.

Operation

On March 13, 1952, a large mass was found in the pelvic colon extensively adherent to the bladder at two distinct points—one in the lower pelvic colon and the other in the sigmoid. The proximal point of adherence was the site of the fistula. The appearances were those of a carcinoma, but the diagnosis was not certain because of some thickening of the mesentery and the extensive length of bowel involved. It was decided to separate the bowel and bladder, partly to help in establishing the diagnosis and partly for access, as the pelvis was largely occupied by the loop of adherent bowel. This meant possible opening into tumour tissue. On cutting across the fistula the bladder was found to be invaded by what appeared to be a carcinoma, but this was still uncertain. It was necessary to leave a hole an inch (2.5 cm.) wide in the bladder. The bowel and bladder were next separated at the lower point of adhesion, leaving a further area at the back of the bladder, possibly the site of malignant infiltration. Most of the pelvic and sigmoid colon and the upper third of the rectum were excised with the usual block of glands. The colon was then slit up and the lesion was clearly seen to be a carcinoma.

The bladder had then to be dealt with. Experience of local excision of malignant vesico-colic fistulae had made me pessimistic of achieving a satisfactory clearance of growth, and in this instance there was so much inflammatory induration of the bladder that it seemed unsafe to try to close the defect in it. I decided on total cystectomy and proceeded to remove the bladder, prostate, vesicles, and gland fields. In addition, a further portion of rectum was removed, together with the whole of the pedicle of the superior haemorrhoidal vessels, thus giving a satisfactory clearance below the lower point of adherence of bowel to bladder. There remained a rectal stump above the levator ani about 1¼ in. (3.8 cm.) in length. After mobilization of the remnant of pelvic colon and descending colon it was possible to make a loose approximation to the rectal stump, and, as there had been wide excision beyond the margin of growth and there was free bleeding at the bowel ends, I proceeded to make a junction.

Prior to anastomosis it was necessary to clear the colon above by milking of faeces still remaining in it. After the bowel ends were joined the ureters were transplanted into the pelvic colon by a submucosal tunnel technique. At the completion of the anastomosis the floor of the pelvis was dry, but gauze was packed on the levator ani. A drainage tube was placed to the bottom of the pelvis, the abdominal wound closed, the rectal sphincter dilated, and a tube stitched into the anus for about 1 in. (2.5 cm.) for possible urinary drainage. The patient was given 2 pints (1,140 ml.) of blood and a pint (570 ml.) of saline during the course of the operation, and was in good condition at the end. The anaesthetic was low spinal, thiopentone, nitrous oxide and oxygen, and enough gallamine triethiodide for the introduction of an endotracheal tube.

Histological Examination (Dr. R. A. Sladden).—"The tumour in the colon is a moderately well differentiated adenocarcinoma, Broder's grade II, invading the muscular coats and at one point penetrating to the serosa. There is no lymph-node involvement found. The bladder wall is thickened to 2 cm. posteriorly by an intense chronic inflammatory reaction. There is no microscopical evidence of spread of growth into the bladder wall in the sections examined. The paravesical lymph nodes show no evidence of metastases."

Further Progress

On March 15 a general anaesthetic was given for removal of the pack. As the patient had not yet passed any urine and was showing moderate distension, the rectal tube was removed. The opportunity was taken of inspecting the ureteric and bowel anastomoses, which were satisfactory, but the intestine, including the colon, was somewhat distended; as it seemed likely that this distension would be

relieved by caecostomy, I inserted a catheter by the inkwell technique. To my surprise nearly 2 pints (1,140 ml.) of urine immediately poured from the caecostomy. I had imagined the patient to be anuric, while all the time the urine had been passing into the bowel, but not past the anastomosis, owing to some local swelling or other mechanical or postural factor which had directed it into the proximal colon.

The blood urea on the fourth day after operation was 124 mg. per 100 ml., but on the seventh day it had fallen to 88 mg. At this stage everything appeared satisfactory, so I went on a belated leave, and had no sooner reached a remote mountainous region of Europe than the patient developed an acute intestinal obstruction. My colleague A. S. Till attended to the patient, operated, and relieved the obstruction, which was due to kinking of small bowel from an adhesion to the pelvic floor. This timely intervention was life-saving. There was one more hurdle in the form of a deep left femoral thrombophlebitis, which responded to treatment with ethyl biscoumacetate ("tromexan"). During the period of complications, when anal control had not become established, great relief from continual wetting, sore buttocks, and a messy bed was achieved by keeping in the anus a catheter which was connected to continuous suction.

Functional Result.—Two and a half weeks after the operation for obstruction the patient had acquired anal control. He now passes one, occasionally two, firm bowel motions a day, and can sleep through the whole night without the need to pass his urine. During the day he can hold the urine for three to four hours, but has been told to pass it every two hours. He has complete control, except occasionally, when it is necessary to pass a large volume of wind.

One year after operation the patient is happy, with no sign of recurrence.

Discussion

It is due to the efforts of Brunschwig (1948) and others that excision of all the organs of the pelvis has become a recognized procedure for carcinomatous disease of the rectum and uterus with marked local spread into adjacent organs. The operation usually demands, in addition, clearance of the pelvic diaphragm and the perineal portions of the bowel and other organs, and the establishment of a pelvic end-colostomy into which the ureters are transplanted, resulting in a "wet" colostomy. This means a constant flow of urine on to the abdominal wall, and the need for a special rubber bag stuck with adhesive plaster to the skin about the colostomy. The procedure has undoubtedly rescued or relieved many patients otherwise doomed to die or suffer, and is still all there is to offer to most of these patients. But, as Appleby (1950) has said, "bilateral ureteric transplant into the bowel in the presence of colostomy produces a chain of miseries all its own, as the vast array of gadgets, plugs, tampons, trick colostomies, and skin-grafted loop protrusions is surely testament." He endeavoured to reduce the urine coming from the colostomy by transplanting the ureters into the caecum, which allowed more water absorption, reducing the flow by 30%; but two-thirds of the urine coming from the colostomy is still a lot.

Others have endeavoured to fashion an artificial bladder from colon or ileum. The possibility of doing this present style of operation had been indicated to me in a personal communication by E. G. Muir, who had spoken of a three-stage procedure, employing a transverse colostomy to defunction the bowel before undertaking the major operation. My preference in non-obstructive colon surgery generally is, so far as possible, for anastomosis without a higher defunctioning colostomy, and in this new operation there seems to be no reason for departing from this principle, though the inclusion of a caecostomy or transverse colostomy of the catheter type at the operation may be advisable for drainage of urine and wind. The procedure described here is applicable in some of the patients in whom, though the disease is widespread, there is no need for removal of levator ani muscles. In this patient the excisions and anastomoses were all done in one stage, even though at the time of the removal of the pack a tube caecostomy was performed, and a further operation was later necessary for small-gut obstruction. But the principle and practice of removal and anastomosis of bowel and ureters in one stage was established.

This case provides an encouraging answer to the question of the subsequent state of anal control when most of the rectum and sigmoid colon is removed, the remaining ends are joined, and both ureters are transplanted into the pelvic colon. In this instance there resulted complete anal control with total nightly continence and daily continence for four hours or more if desired. So it appears that the functional result for ureteric transplantation is likely to be the same whether or not the colon is resected. Most patients with ureteric transplants into the colon adapt themselves rapidly to the altered function and are fairly comfortable.

There are many patients in whom the extent of spread will rule out resection and anastomosis of bowel, whether or not an adjacent organ is invaded. But there is accumulating evidence for the satisfactory result of excision with anastomosis of rectosigmoid lesions when the growth is high enough above the levator ani muscle. There is no point in reviewing this work here. It is sufficient to say that, if the lesion in the bowel is at a high enough level and the manner of involvement of an adjacent organ does not preclude preservation of a stump of rectal tissue above the levator ani, then it may be possible to do an excision of bowel with anastomosis, followed by ureteric transplantation into the bowel above the anastomosis. Even should one or two distant secondaries have arisen from carcinoma of the rectum involving the bladder, this procedure could give great comfort at not undue strain or risk to a patient with severe cystitis, perhaps diarrhoea, and intolerable pain. Those who have practised the procedure of block excision of the pelvic organs have described how remarkably quickly the pelvis is cleared when both the internal iliac arteries or their anterior branches are tied.

Similarly, in carcinoma of the uterus confined to the pelvis but spreading forwards into the bladder and backwards to the rectum, it would seem justifiable to try this less dehumanizing operation if excision can still be adequately radical.

Cystectomy and transplantation of ureters in one stage, for which I pleaded (Moloney, 1947) with others, has now become the popular method of conducting this procedure, and the older multiple-staged techniques, wearying alike for patient and surgeon and probably no safer in the end, are mostly outmoded. Now that a one-stage procedure for cystectomy and rectosigmoidectomy with anastomosis has been shown to be possible, I make this plea that, where indicated, it be given a fair trial.

Summary

An operation is described for vesico-colic fistula due to a carcinoma of the rectosigmoid colon, in which the affected portion of bowel and the bladder were excised, with immediate anastomosis of bowel to bowel and ureters to pelvic colon, thus avoiding a "wet" colostomy. The functional result is excellent, the patient being dry all night and capable of holding his urine for four hours by day if necessary.

A plea is made for trying this procedure, where indications allow, to avoid the unpleasantness of life with a "wet" colostomy.

References

Appleby, L. H. (1950). *Proc. roy. Soc. Med.*, **43**, 1071.
Brunschwig, A. (1948). *Cancer*, **1**, 177.
Moloney, G. E. (1947). *Brit. J. Surg.*, **35**, 91.

A METHOD OF ANAESTHESIA FOR TONSILLECTOMY

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Operation for excision of tonsils and adenoids is one of the commonest surgical procedures both in this country and on the continent of America. In this country alone 1,500 children are operated on each week (Report of the Chief Medical Officer of the Ministry of Education).

The predominant age group of patients is between 4 and 10 years. The operation is, however, commonly performed in adolescents and adults. Anaesthesia for these operations has become almost standardized. Local analgesia, a common practice on the continent of Europe, has found little favour here. Whereas endotracheal intubation is regarded as the *sine qua non* in older children and adults, opinions are divided regarding its advisability in younger children.

The methods described in this paper are presented not for their originality but for the ease and minimal disturbance to patient, surgeon, and anaesthetist.

Present Series

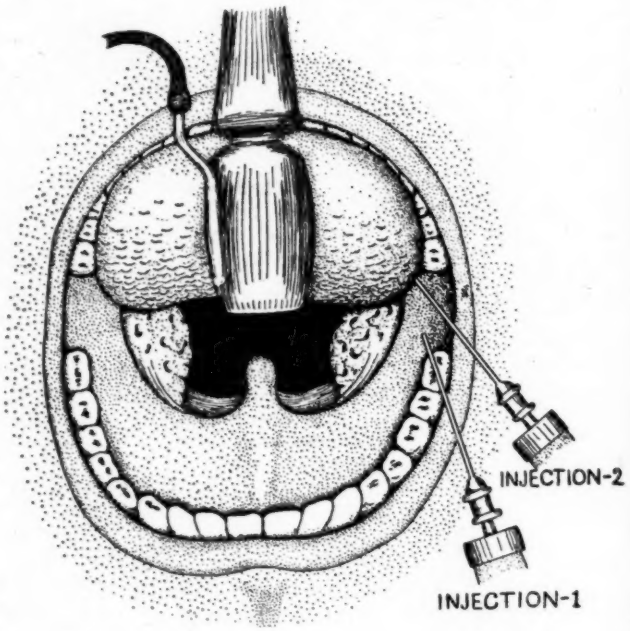
Material.—Up to date over 1,400 patients have been operated on, mainly at the South-western Hospital. Of these, 137 (9.8%) were over 10 years of age, 6 (0.4%) were adults, and 10 (0.7%) were adolescents aged between 15 and 18, who, because of their build and weight—about 8 st. (50.8 kg.)—were anaesthetized by the same method as the adults.

No mortality or morbidity occurred that could conceivably be connected with the method of anaesthesia employed.

Premedication plays a great part in the success of the method, and therefore accuracy in its application is insisted upon. Children between 4 and 9 years (assuming their weight to be broadly within normal limits) receive, one hour before operation, 1½ gr. (0.1 g.) of quinalbarbitone ("seconal") and 10–15 mg. of pethidine, with 1/150 gr. (0.43 mg.) of atropine by injection. Those between the age of 10 and 18 years are given 3 gr. (0.2 g.) of quinalbarbitone and 15–25 mg. of pethidine, with 1/200 gr. (0.32 mg.) of atropine. Adults receive 3 gr. (0.2 g.) of quinalbarbitone, 25–50 mg. of pethidine, and 1/150 gr. (0.43 mg.) of atropine. Pethidine for children is thus given at approximately 3–3.5 mg. per stone (0.47–0.55 mg. per kg.) of body weight. The well-established analgesic and antispasmodic action of pethidine when combined with the hypnotic effect of quinalbarbitone makes the induction of anaesthesia by means of the sequence of inhalational agents (nitrous oxide with oxygen–trilene–ether) rapid and smooth.

With the above premedication patients arrive in the theatre fast asleep, and pass, with judicious induction, from sleep, without waking up, into anaesthesia within a matter of two minutes. Those who arrive in the theatre conscious but drowsy are not apprehensive and readily co-operate in "blowing up the red balloon."

Induction is achieved by allowing nitrous oxide to flow at the rate of 10 litres a minute without the mask touching the face. Sense of smell is lost in two or three breaths, and a trickle of "trilene" is added. The mask is then lowered to the face and nitrous oxide is adjusted to 6 litres, and oxygen, 2 litres, is added, the child remaining pink throughout. The expiratory valve is closed and the bag emptied two or three times to eliminate some of the lung nitrogen. Three breaths later an oral airway is introduced at the slightest suggestion of obstructed airway, and is surprisingly well tolerated; a trace of ether is then added to the mixture. The expiratory valve is now slightly opened and the bag is very gently compressed, assisting respiration. The patient is now wheeled into the theatre, and whilst he is being placed on the table (with head-down tilt of about 5 degrees) and the towels are being draped in the thyroid position the ether is allowed to flow more freely; at no time need the gases bubble through the ether.



It will be found that the lower jaw is sufficiently relaxed for the Davis gag to be placed in position. The harness is not used, the gag being supported manually.

Experience has taught us that the above technique provides adequate anaesthesia for tonsillectomy and adenoidectomy in children up to the age of 10.

In children of 10 years and over greater concentration of agent or agents employed and/or intubation would be necessary to achieve the same purpose. Instead of resorting to either of the above means, we find it advantageous to cut off the access of traumatic stimuli, leaving the plane of general anaesthesia light. Therefore in older children the method is combined with infiltration of the vicinity of the tonsil with 1% lignocaine hydrochloride without adrenaline. This is done by the surgeon as described below.

Infiltration amounts to selective blocking of two nerves, the lesser palatine and the glosso-pharyngeal. When the gag is in place the right tonsil is grasped by a pair of Luc's forceps held in the left hand, and the needle is inserted to a depth of 0.5 cm., 1 cm. behind the last lower molar tooth, keeping outside the fold formed by the anterior border of the palato-glossus muscle. After trial aspiration, 2 ml. of 1% lignocaine hydrochloride is injected. This injection blocks the fibres entering the tonsillar plexus via the lesser palatine branch of the maxillary division of the trigeminal nerve. A second injection of 2.5 ml. of 1% lignocaine hydrochloride is made into the lateral border of the tongue adjacent to the lower pole of the tonsil into the loose

pericapsular areolar tissue overlying the pharyngeal constrictor muscle. This injection blocks the tonsillar branch of the glosso-pharyngeal nerve. The second tonsil is then similarly injected. To allow time for the injection to take effect adenoidectomy is performed first. With practice the blocking can be performed in about one minute if a long needle —4½ in. (11.5 cm.)—is employed attached to a 10-ml. syringe.

For adults, and for adolescents of about 8 st. (50.8 kg.), pethidine is given as in the case of children, or as an alternative intravenously after induction is effected by thiopentone (about 0.5 g. 5%). If need be, fractional doses of thiopentone are added until the block takes effect. The Davis gag is inserted and nitrous oxide and oxygen (6 litres and 2 litres respectively), with a trace of trilene, are allowed to flow through the gag. No ether is used. Blocking infiltration is then performed by the surgeon. No laryngeal spasm has occurred during the injection.

Discussion

The combination of quinalbarbitone with pethidine was used by Poe and Karp (1948) as a basal narcotic for children. In this series smaller doses have been used. Induction with nitrous oxide, oxygen, and trilene makes the introduction of ether rapid and easy. Surprisingly little ether is required to allow the Davis gag to be inserted and the tonsils dissected.

Consciousness after the operation is regained within a period varying from a few minutes to a quarter of an hour. After a brief period of restlessness on awakening and a single act of vomiting, children relapse into sleep.

The feature of this method is that intubation for tonsillectomy becomes completely redundant, regardless of the age of the patient. However expertly performed, intubation is regarded by some as an additional hazard. Dingley (1943) points out the contraindications against intubation from the rhinological point of view. These are connected with the possible infliction of trauma to the structures encountered and/or spread of infection.

In addition, with the method employed the cough reflex is never absent during the operation. This is demonstrated by allowing blood to overflow into the larynx. To prevent this happening the table is tilted slightly downwards, thus obviating the necessity for throat packing, with subsequent soreness of the throat. Blood is mopped up by gauze swabs. Capillary oozing is scanty.

When infiltration is used the tonsils are moved by the fluid towards the midline and are easier to dissect because of the presence of the fluid in the capsule plane.

It has been stated that the chief objection to the use of local analgesia for tonsillectomy is the increased risk of sepsis. On the other hand, Morey (1943) performed more than 2,300 tonsillectomies under local analgesia alone, injecting into each side as much as 25 ml. of fluid without untoward results. It will be noted that the injection described here is paratonsillar and not intratonsillar; no adrenaline is used and the amount of fluid injected is small (a total of 4–5 ml. on each side). In this series of 137 cases healing of the tonsillar bed was unaffected, and the general recovery was not delayed.

Summary

A method of anaesthesia for tonsillectomy based on over 1,400 cases is described.

In young children premedication consists of quinalbarbitone and pethidine, producing a state of basal narcosis or adequate sedation. Inhalational agents (nitrous oxide and oxygen, trilene, ether) provide adequate anaesthesia in smaller concentration than otherwise.

In children of 10 and over and in adults the method is combined with the blocking of the lesser palatine and the glosso-pharyngeal nerves.

Advantages of the method are discussed.

Intubation for tonsillectomy is dispensed with in patients of all ages.

We wish to thank Dr. J. C. Blake, physician-superintendent, South-western Hospital, for his ready co-operation in facilitating our work.

REFERENCES

Dingley, A. R. (1943). *British Medical Journal*, 1, 693.
Morey, G. W. (1943). *Lancet*, 2, 794.
Poe, M. F., and Karp, M. (1948). *Curr. Res. Anesth.*, 27, 88.

AORTIC OCCLUSION IN INFANCY

BY

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Occlusion of the aorta is rightly regarded as a rare but highly fatal condition. Most recorded cases have occurred in adults suffering from auricular fibrillation, from bacterial endocarditis, or from a mural thrombus following myocardial infarction or associated with atheromatous changes. Gross (1945) has cited 37 cases of severe arterial occlusion in infancy, the most common arterial location being in the lower limb. Rothstein (1935) quotes two cases of saddle embolus in 10-day-old infants, following on umbilical sepsis.

The present case of saddle occlusion at the aortic bifurcation in an 11-months-old child appeared to show enough uncommon features to warrant recording.

Case Report

An 11-months-old male infant was admitted to hospital on December 21, 1951. Although premature at birth, he had developed and thrived consistently until his present illness. Six days before admission the child developed features of upper respiratory infection. He was seen by a doctor, who prescribed a cough mixture. His condition improved, but on the fifth day of illness he became very restless and irritable. He refused his feeds, and at this stage sulphadiazine was prescribed. At 10.30 a.m. the next morning the child's father noted that the right foot and ankle were white and cold.

On admission that afternoon at 3 p.m. he was an extremely ill child with an ashen-grey cyanosed appearance. His temperature was 102.4° F. (39.1° C.), pulse 140, and respirations 50. Examination of the chest disclosed no cardiac abnormality, but diffusely scattered rales were present in both lung fields, most prominently at the right base. The right lower limb was cold, limp, and deathly pale, with mottled areas of marbling extending from the toes to the middle of the thigh. The dorsalis pedis, posterior tibial, popliteal, and femoral arteries were impalpable on the right side. The right knee- and ankle-jerks were absent. The left limb was normal, all pulses being palpable, and all reflexes were present. A small area of ecchymosis, 2 cm. in diameter, was noted on the surface of the right elbow.

The child was placed in an oxygen tent and penicillin therapy was given to control the bronchopneumonia. The right lower limb was exposed to room temperature, and at 4 p.m. a right paravertebral block was performed with 10 ml. of 0.5% procaine hydrochloride in an attempt to open up the collateral vessels. At this stage the child's general condition prevented any more heroic measures. No change in the condition of the leg was noted.

At 8.30 p.m. an intense uncountable tachycardia occurred and the abdomen became distended; bowel sounds were absent. An occlusion of the superior mesenteric artery, causing a paralytic ileus, was envisaged. At 11 p.m. it was noted that the toes of the left foot had become icy cold and pale. The left femoral and popliteal arteries were palpable, but the left dorsalis pedis was impalpable. The abdominal distension gradually resolved, bowel sounds returned, and the child passed a motion mixed with blood.

At 9 a.m. on December 22 marbling of the left foot was present, extending to the ankle. The condition of the right limb remained unchanged. As the child's general condition had improved slightly it was decided to explore the aortic bifurcation despite the fact that 24 hours had elapsed since the onset of vascular inadequacy in the lower limbs.

Operation.—Under general anaesthesia the aortic bifurcation and the iliac tributaries were exposed by a midline subumbilical extraperitoneal approach. Pulsation was absent in the right common iliac but was present in the left iliac vessels. The thrombus was palpable, extending from the aortic bifurcation along the whole extent of the right common iliac and partially into the left common iliac vessels, partially obstructing the latter. The right common iliac artery and its tributaries were dissected out and rubber catheters passed round the external iliac and the common iliac arteries and aorta. A small vertical incision was made in the right common iliac artery, and the clot extruded itself and was withdrawn. Further extensions of the clot were milked and sucked out, proximally and distally, until brisk gushes of arterial bleeding occurred. The clot was smooth and not adherent to the arterial wall. The opening in the vessel was closed with five interrupted waxed-silk sutures. After suture the right common iliac artery was distinctly narrower than the left, but active pulsations were transmitted. The wound was then closed in layers.

The child's general condition remained unchanged and no appreciable improvement was noted in the limbs as compared with the pre-operative state. The blood-coagulation time, estimated at 9 p.m., was 7½ minutes. Five thousand units of heparin was given intravenously. The child died at 3.25 a.m. on December 23.

Post-mortem Findings.—The heart disclosed no abnormality, but the lungs showed marked bronchopneumonic changes. The small intestine was covered with multiple small haemorrhagic infarcts, but no clot was found in the superior mesenteric artery. The thrombus removed from the aortic bifurcation was red in colour, and consisted of hyaline material containing red cells and granulocytes.

Discussion

All writers on arterial occlusion in infancy stress the importance of sepsis in its causation, but, as Gross correctly points out, overwhelming infection in infants may cause multiple areas of cutaneous and deep-tissue necrosis representing focal areas secondary to pyaemia or septicaemia, but only rarely will occlusion of larger vessels occur without the presence of endocardial vegetations.

Thrombosis of the umbilical and hypogastric arteries in the neonatal period is a physiological mechanism which may progress abnormally against the blood current into the common iliac artery. By progression the thrombus may extend even into the lower portion of the aorta. Arterial obstruction in the newborn should suggest this pathological sequence.

The presence or absence of a congenital heart lesion must always be ascertained; arterial embolism in such cases carries a bad prognosis, as the likelihood of repeated episodes is ever present. In the presence of such a lesion, vascular accidents are fostered by any severe illness which may induce dehydration, haemoconcentration, and augmentation of blood coagulation.

In the above case the necropsy findings excluded a congenital heart lesion or endocardial vegetations—the latter having been considered clinically as the cause of the multiple emboli. It had been thought that the first embolus had impacted in the right common iliac artery, with retrograde extension to the aortic bifurcation, and that a second embolus involved the superior mesenteric artery. The absence, however, of a common source for the emboli strongly suggests that the arterial occlusions were due to separate thrombotic processes complicating a severe bronchopneumonia.

The collateral circulation in infancy must be extremely adaptable, with great potentiality for compensatory dilatation. Thus sympathetic nerve block is a useful measure. The administration of heparin may be difficult in infancy, but ethyl biscoumacetate ("tromexan") may prevent propagation of an established thrombus.

Embolectomy or surgical evacuation of the thrombus within 6 to 10 hours is indicated if the infant's limb is in danger, but amputation, even if indicated, should be deferred for as long as possible during this time, every effort being made to augment the impaired circulation.

We are indebted to Dr. M. L. Thomson and Mr. H. M. Goldberg for permission to report this case and for their advice and encouragement.

REFERENCES

Gross, R. E. (1945). *Amer. J. Dis. Child.*, **70**, 61.
Rothstein, J. L. (1935). Ibid., **49**, 1578.

Medical Memoranda

Pilonidal Sinus of the Suprapubic Region

Professor Ian Aird (1952) reports a case of pilonidal sinus of the axilla and states that this makes the sixth site of pilonidal suppuration, the five sites previously recorded being the sacro-coccygeal region, the perineum, the barber's hand, the sole of the foot, and the umbilicus. The following case report is of interest in that the patient presented a lesion in the suprapubic region which looked like and behaved like a pilonidal sinus. Histologically, it was a simple dermoid. Professor Aird's article stimulated the recording of this case of pilonidal suppuration at a site which must be rare, as it does not seem to have been reported previously.

CASE REPORT

The patient, a woman aged 35, was admitted to hospital on January 30, 1952, with a history of having had, in the suprapubic region, a swelling like a boil, which pointed and burst, then leaked pus for some weeks and finally regressed, only to recur and go through the same cycle again and again. The history was of two years' duration. Fourteen years before she had had a sacro-coccygeal pilonidal sinus excised. Following this operation the wound had healed soundly and there had been no recurrence of suppuration at that site.

On examination a sinus with a pinhole orifice was observed in the middle of a shallow depression ¼ in. (6 mm.) in diameter, in the midline immediately above the symphysis pubis. On pressure a small bead of pus was expressed from the orifice.

On January 31 the sinus, along with a cyst with which it communicated, was excised through an elliptical incision. The cyst extended downwards for about 1½ in. (3.8 cm.) in the midline, its most distal part lying superficial to the symphysis pubis. A small tuft of hair was found inside the sinus. On February 6 the patient was discharged with the wound soundly healed.

The histological report on the excised sinus and cyst was as follows: "Sections show a simple dermoid lined with squamous epithelium and containing a few hair follicles. There is a thick fibrous wall with a little subacute inflammatory change in parts."

COMMENT

In this case, as in Professor Aird's, there was a previous history of operative treatment for a pilonidal sinus in the sacro-coccygeal region. The clinical and histological appearances of the sinus were those of a pilonidal sinus. It is probable that the origin in this case was a dermoid cyst occurring at a point of embryological fusion. Being a hair-bearing dermoid, it formed a hair-bearing sinus. It is therefore etymologically correct to define it as a pilonidal sinus.

It is suggested that to the six previously recorded sites of pilonidal suppuration may be added a seventh, the suprapubic region. It is also suggested that pilonidal suppuration could occur in any place where dermoids are apt to occur—that is, at points of embryological fusion—provided that the cyst contained hair follicles in its lining membrane. It may be that the term "pilonidal sinus" is usually reserved for the sinus occurring in the sacro-coccygeal region, and that similar sinuses occurring elsewhere are not labelled as pilonidal sinuses but given names such as suppurating dermoid cysts and so have not appeared in the literature as additional sites of pilonidal suppuration.

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REFERENCE

Aird, I. (1952). *British Medical Journal*, **1**, 902.

Deaths of Two Patients Treated by Phenylbutazone

Agranulocytosis and haemorrhage, usually from the gastro-intestinal tract, are the principal recognized toxic reactions caused by phenylbutazone ("butazolidin"). The drug is contraindicated in the senile, the hypertensive, and those with a history of peptic ulcer, oedema, or other manifestations of heart failure. Four deaths attributed to the drug were recorded recently (*British Medical Journal*, 1952; Davies and others, 1952). In one the cause was haemorrhage from multiple ulcers of the stomach, and in two agranulocytosis was responsible. The following two cases were both the subject of a coroner's inquiries.

CASE 1

A woman aged 65 had suffered from rheumatoid arthritis for 17 years. This had progressed steadily, and before the administration of phenylbutazone she had been confined to her chair and suffered much pain. After being warned of the risks the patient agreed to phenylbutazone therapy, and one 0.2-g. tablet thrice daily was prescribed. Her pain was relieved and she was able to walk better. After 15 days' continuous treatment she complained of severe pain in the right loin, with radiation to the groin, and her urine was heavily contaminated with blood She died the following morning.

Necropsy.—This was made 53 hours after death. The body was that of a small, frail old woman with blue, swollen ankles. The lower end of the oesophagus was oedematous and contained a subacute ulcer ½ in. (1.3 cm.) in diameter. The stomach was normal, but on the anterior wall of the duodenum, 2 in. (5 cm.) distal to the pylorus, there was a perforation caused by the rupture of a small subacute ulcer ¼ in. (0.6 cm.) in diameter. There was no sclerosis in relation to either ulcer, and no evidence of present or past ulceration in the remainder of the alimentary canal. The left pleural cavity was obliterated by old fibrous adhesions, and the right cavity contained about 1 pint (570 ml.) of clear serous fluid. The upper lobes of the lungs were normal, but both lower lobes were partly collapsed and very oedematous. The pericardium was bound to the heart by old fibrous adhesions in several places, and there was slight thickening of the muscular walls of both ventricles. The kidney substance was pale and the cortex was notably reduced. The capsules stripped with some difficulty, leaving a coarsely scarred surface. The adrenal glands showed complete loss of cortical lipid, and a diffuse fibrino-purulent peritonitis originating from the duodenal perforation caused matting of coils of intestine. Death was due to peritonitis following perforation of the duodenum due to peptic ulcer associated with phenylbutazone therapy.

CASE 2

A woman aged 71 suffered from rheumatoid arthritis, and, after being warned of the risks, agreed to treatment by phenylbutazone. One 0.2-g. tablet was taken by mouth each day for a week, after which she felt much better, and the dosage was doubled to 0.4 g. a day for a second week. At the end of this fortnight's treatment she did not feel well and stayed in bed. The following day she telephoned to her doctor at 6 a.m. and complained of severe pain in the left hip. Her doctor visited her immediately, gave her an injection of morphine, and requested an enema to be given by the district nurse. At 9.15 a.m. she was found on the floor of her bedroom; she said that she was unable to get back to bed, and again complained of pain in her left hip and down her left side. She died at 2.15 p.m. the same day.

Necropsy.—This was made 26 hours after death. The body was that of an obese edentulous old woman with swollen finger-joints. The left flank and thigh were swollen and discoloured and the overlying skin was peeling or raised in large blebs. The superficial vessels of the neck presented a "marbled" appearance, and the abdomen was distended. No break in the skin was observed in the putrid areas or elsewhere. The heart muscle was pale and flabby, but the valves and chambers were normal. The main vessels were filled with frothing blood, and the intima showed intense haemolytic staining. The lungs were uniformly engorged. The peritoneal cavity was distended by foul-smelling gas, and the muscle between the spine and the left kidney was soft, black, crepitant, and friable. This gangrene involved the whole of the left psoas and iliacus muscles and extended half-way into the quadratus femoris muscle group of the left thigh. The stomach and both small and large intestines were normal and showed no naked-eye evidence of ulceration in the mucous lining, and the loose connective tissue behind the descending colon was apparently normal. The kidneys showed marked toxic pallor of the cut surface, and the bladder was empty and normal. The cut surface of the spleen was pale, soft, and putrid, and that of the liver very pale and dotted with small gas bubbles. The adrenal glands showed cortical pallor, and the remaining abdominal organs were normal. Death was due to gas gangrene.

DISCUSSION

There can be no doubt that death in Case 1 was directly contributed to by phenylbutazone. Shortly before death there was a haemorrhage from the genito-urinary tract for which no organic cause existed, and the two alimentary ulcers had acute characteristics. There was no history of indigestion referable to the stomach or duodenum, though six months before death this patient complained of pain at the lower end of the sternum about two seconds after swallowing. Radiological examination of the oesophagus was negative, and the symptoms subsequently passed off. The oesophageal ulcer found at necropsy was too recent to have caused these symptoms, though there may well have been a previous oesophagitis, with or without superficial transitory ulceration.

The mechanism leading to death in Case 2 is obscure, since the disease was obviously established before the injection of morphine into the right upper arm. Cases of gas gangrene in which the infecting organism was presumably derived from the bowel have been reported, but they are

rare, and in this instance there is no indication of how the organisms gained a "bridgehead" in the muscle. It is, however, possible that in some cases of clostridial myositis following a wound or an injection the infecting organism has been derived from the bowel rather than by inoculation from the exterior of the body. There was a rather suggestive latent period of at least eight days in the case reported by Shaw and Evans (1953), though admittedly delays of longer than five days may occur even in grossly contaminated wounds.

Direct evidence that phenylbutazone contributed to death is lacking. However, in view of the rarity of the condition, and the known effects of phenylbutazone on the continuity of the gut mucosa and on the circulating white corpuscles, it is difficult to dissociate the drug from some part in the initiation or spread of the gangrene or terminal septicaemia.

Since these two cases, both treated in general practice, two other fatalities have come to my notice. Both were instances of death due to perforation of peptic ulcer during phenylbutazone treatment. It should be noted that in Case 1 the perforation was unsuspected, nor was the cause of death clinically apparent in Case 2. The possibility of analgesic properties masking signs and symptoms is therefore of some importance.

It seems pertinent to iterate that, apart from the known contraindications, phenylbutazone should never be given without *regular and frequent* clinical assessment of the patient and appropriate white-cell counts.

Assessment of the precise risks attached to new drugs is never easy, and risks are not necessarily as great in hospital as they are in general practice. It is perhaps desirable that statutory post-mortem examinations should be held on all patients dying while treated by any new drug within a specified time of its inception *even if there is no prima facie reason for supposing death to be attributable to treatment.*

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REFERENCES

British Medical Journal, 1952, 2, 1401, 1427.
Davies, H. R., Barter, R. W., Gee, A., and Hirson, C. (1952). *British Medical Journal*, 2, 1392.
Shaw, S., and Evans, W. E. (1953). Ibid., 1, 429.

A Case of Subserous Duodenal Haematoma

A case of this condition due to non-penetrating and apparently trivial injury is reported because a search of the literature has not brought to light any record of a similar case.

CASE REPORT

A thin boy aged 9 was admitted to hospital on April 9, 1952, for abdominal pain and vomiting. Five days before admission he had "gone over" the handlebars of his bicycle; he thought he had fallen mainly on his left side, and had had a small abrasion of the left temple and left leg. From his own and his parents' account of the injury, it seems to have been regarded as trivial, and he was riding his cycle again a short time after the accident. He complained of some abdominal pain, but this was not severe and passed off in a few hours. Two days later he was seized with a sudden abdominal pain of such severity that he had to be put to bed; a hot-water bottle was applied to the abdomen, which apparently relieved him and he slept, but he woke at midnight and vomited food. Pain was felt in the central abdomen and remained in this area. The next day his general condition became worse; the abdominal pain was more severe, and vomiting and retching continued all day. His bowels were not open. His doctor decided that the condition was probably appendicular colic. He was kept in bed and given fluids and "sulphatriad."

On the day before admission he seemed to be slightly better: the pain was less severe, but vomiting and retching continued. There was a slight rise of temperature and pulse rate. His bowels had still not been open. On the day of admission the pain had again increased and vomiting and retching were very frequent. The doctor noted a slightly raised temperature, but the pulse rate had risen further.

Apart from the usual childhood diseases he had always been well.

On admission the patient was slightly flushed and seemed to be in some distress. His temperature was 98.6° F. (37° C.), pulse 74, respirations 22. The tongue was coated and dry, and there was some fetor oris. The abdomen was slightly distended but moved freely with respiration. There was no evidence of bruising or abrasion of the abdominal wall. The boy pointed to the site of pain as immediately below the umbilicus, and there was some guarding and tenderness in this region. Hard faeces could be felt in the descending colon. No other abnormality could be detected on abdominal examination. On rectal examination hard faeces were felt; there was no tenderness or induration. Routine urine examination showed no abnormality. The haemoglobin was 15 g.%; total leucocyte count, 16,200 (polymorphonuclears 84%, lymphocytes 16%); bleeding-time, 5½ minutes; clotting-time, 9 minutes. A straight *x*-ray film of the abdomen showed that the stomach contained a considerable quantity of gas.

The child was placed under observation and given fluids only by mouth. He vomited twice soon after admission; each vomit was of a few ounces and contained mucus and flecks of altered blood. An intravenous drip of glucose–saline was set up, a Ryle's tube passed, and gastric suction started; about 1 pint (570 ml.) of a "coffee ground" type of gastric fluid was aspirated. Further examination of the abdomen about eight hours later revealed a fixed ill-defined mass in the midline above the umbilicus.

On the morning of April 10 the boy's general condition had improved, and it was decided to perform a laparotomy to find the cause of what was obviously a high small-intestine obstruction. The abdomen was opened through an upper midline incision. The mass was found to be a gross enlargement of the second, third, and fourth parts of the duodenum and the first 4 in. (10 cm.) of the jejunum. At first sight the mass appeared to be gangrenous, being blue-black. Further examination showed that there was a very large subserous haematoma: 4 oz. (114 ml.) of fluid blood was aspirated from beneath the serous coat, and after incision of the serosa a great quantity of clot was evacuated with the finger. The underlying muscle coat appeared to be intact, but the presence of such a large clot had completely closed the lumen of the duodenum. The serosa was left unsutured and the abdomen closed without drainage.

Convalescence was slow but uneventful, and the patient was discharged from hospital six weeks after operation. When seen one month and three months after discharge he was very well. He had gained weight and was taking normal diet. No mass could be felt on abdominal examination.

COMMENT

Although there is no clear history of injury in this case, it is reasonable to assume that the lesion was caused by abdominal injury at the time of the accident. That the force of the blow was slight is evident from the fact that neither the child nor the parents were definitely aware of it, and from the absence of bruising of the anterior abdominal wall. The injury seems to be related to the blast injuries of the abdomen seen in the late war, and the effects of the injury were maximal in that area because of the immobility of the second, third, and fourth parts of the duodenum and the relative immobility of the duodeno-jejunal flexure.

I wish to thank Dr. C. D. Agassiz, physician-superintendent of Queen Mary's Hospital for Children, and Mr. A. M. Desmond, who performed the operation, for permission to publish this case.

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Reviews

MEDICAL BIBLIOGRAPHERS

The Great Medical Bibliographers: A Study in Humanism. By John F. Fulton. (Pp. 83, with 5 appendices, index, and 37 figures. 32s.) Philadelphia: University of Pennsylvania Press. 1951.

The wine of Dr. Fulton's providing needs no bush. To one who loves books, without any vestige of knowledge of bibliography, his account of *The Great Medical Bibliographers* has brought vividly back to memory his delightful pen-picture of the three wise men—Welch, Arnold Klebs, and Cushing—toiling up an Apennine pass "bursting with the erudite gossip of the ages." As a young graduate John Fulton had come to England to work under Cushing's old teachers, Sir Charles Sherrington and Sir William Osler, *quibus ille studiis ab ineunte anno imbutus* he became enamoured of the humanistic traditions of Europe's scholar-physicians, started then to collect old books, and, in his own words, "has been at it ever since." To-day, his term of office as Sterling Professor of Physiology at Yale having expired, he is the fortunate director of that university's medical historical library, founded on the joint bequest of Cushing's, Klebs's, and his own collections. "Thrice happy men are they whose Nature sorts with their vocations."

How can one with no pretensions to the bibliographer's *expertise* proceed to review this book? Simply by trying to convey some small share of the pleasure its reading has given him. For Dr. Fulton wears his learning as lightly as ever cavalier wore cloak, conveying with enviable ease through text and footnote the pleasure that may be found in the collection and collation of ancient texts. To him, as collector and connoisseur, bibliography is "the noble art of describing useful and beautiful books"—a happier description than any to be found within the covers of the *Encyclopaedia Britannica*. His enthusiasm is infectious.

In a memorable passage Harvey Cushing has described the febrile state induced by handling a calf-bound volume (1542) published by Etienne Dolet,

> "the unfortunate young Renaissance scholar, contemporary and friend of such as Erasmus and Rabelais, who lived in Lyons when Lyons was a place to live in, who published eighty books, and for three words which left his meaning dubious went to the stake and was burned with his books."

Inscribing his book to the memory of three great medical bibliographers—Conrad Gesner, whom Osler named as the father of bibliography, Albrecht von Haller, in whose soul burned the fire of incessant industry, and John Shaw Billings, whose legacy to medical scholars has been the *Index-Catalogue* of the Surgeon-General's Library at Washington—Dr. Fulton takes his readers straight to sixteenth-century Lyons. Texts then were few, and books both new and rare, but the printers Gryphius and Dolet, for whom Champier, Canappe, and Rabelais—humanist physicians all three—translated and corrected the ancient texts, made their city the first intellectual centre of France. On then from Lyons to Zurich, where Gesner spent his youth poring over the literature of learning as he compiled his *Bibliotheca universalis*. Dr. Fulton's brief account of the scholar rising from his table to tend his ailing wife, as poor and young as he, explains Osler's affection for him.

Through the sixteenth and seventeenth centuries collections of books were private, made by wealthy practitioners only. On their death the collections were either bequeathed to institutions or sold by auction. Printed sales catalogues of "vendible books" first appeared towards the end of the seventeenth century, and copies are still extant of Jean Riolan's collection (1654), of Sir Kenelm Digby's (1665), and of the 20,000 books belonging to Dr. Bernard, at whose sale sixteen Caxtons were sold for five shillings apiece. Such catalogues are of value to-day as evidence of the medical interests of the time or in tracing the provenance of rare books. With the growth of hospitals and medical societies in the eighteenth century came the growing demand for libraries, biographies, and dictionaries.

If, as Butterfield will have it, the seventeenth was the century of the *philosophes*, the eighteenth was as definitely that of the *encyclopédistes*. Greatest of these was the amazing Haller, who as a precocious child of 8 had written 2,000 potted biographies of men of history, and at 10 had completed a Greek lexicon. These were the forerunners of the encyclopaedic work of his maturity: the monumental bibliography of physiology in nine volumes, and his four great *Bibliothecae* of botany (1771), of surgery and anatomy (both in 1774), and of medicine (1776).

And so, not failing in tribute to many lesser luminaries, we are brought down to our own days, in which the expansion of medical literature has surpassed the energy of the individual bibliographer. Even the *Index Medicus* is in arrears, and the *Index-Catalogue* of Billings's creation has had to suspend publication, to the consternation of librarians the world over. Choulant and Osler have been known in person to many who will read this fascinating book, and Geoffrey Keynes is happily with us still to carry on the humanist tradition, working *manu sua* as did his forerunners to the delight of all literate men.

"A collection of books is a university, and the custodian of books is necessarily a teacher." They are the words of Osler, who made old books, and the men who wrote them, live. His Bibliotheca is to-day a Canadian shrine, tended with loving care by his nephew. And through these Transatlantic collections, from Montreal and Baltimore, through Boston, New Haven, and Washington, runs J. C. Bay's "golden thread" which connects all members of a noble lineage back to the little house in Zurich in which Gesner worked and died. The weaving of the thread has been the task of the bibliographer. How fascinating the task, whether of weaving or following, Dr. Fulton's pages most eloquently tell.

WM. DOOLIN.

POLIOMYELITIS

Poliomyelitis. By W. Ritchie Russell, C.B.E., M.D.(Edin.), M.A.(Oxon.), F.R.C.P.Ed., F.R.C.P.Lond. (Pp. 84; 20 figures. 14s.) London: Edward Arnold. 1952.

It is refreshing to read a book on anterior poliomyelitis written by an author conversant with modern trends in neurophysiology and versed in the clinical vagaries of diseases affecting the central nervous system. The book is short, and certain aspects of the disease are scarcely mentioned. There is very little, for instance, about the method of spread of infection. Possibly this was omitted as being outside the author's personal experience, but it is a pity that he does not say more about the morbid anatomy, in which interesting work has been done in the past few years. The account of the clinical features of the acute illness is admirable, and Ritchie Russell makes clear the nature of the "muscle spasm," a term which has been used in such varying senses in the literature of poliomyelitis. He notes that muscle fasciculation may be an important sign in the pre-paralytic phase, occurring in muscles which are likely to become weak during the succeeding 24 hours.

Two-thirds of the book are devoted to the treatment of the disease, about which Ritchie Russell has obviously thought deeply. His account of the importance of postural drainage in bulbar poliomyelitis, and of the use of the respirator in respiratory failure, is of great value, and explains several points which were previously by no means clear to the reviewer. The most controversial feature of the book concerns the methods advised for the treatment of weak or paralysed muscles. By now Ritchie Russell's work on the importance of strict rest in the pre-paralytic stage is generally accepted, but there is likely to be some disagreement with his opinion about treatment when the acute phase is over. He advocates passive movements from the first appearance of paralysis to prevent contractures in

the opposing muscles, avoidance of splints so far as possible, and, within two weeks of the onset of paralysis, progressive active movement to the point of physiological fatigue. He has not been able to confirm that deliberately induced fatigue does any harm to weak muscles in the recovering stages of poliomyelitis, but he emphasizes that research is needed to find out the best method of exercising weak muscles under different conditions.

This is the most stimulating work on poliomyelitis which has appeared for years. Possibly some of the author's ideas on the treatment of weak muscles will not be proved to be correct, but the book should encourage all who treat patients suffering from the disease to think again about treatment. The whole theme of the book, and the unsolved questions which it poses, emphasize the need for special centres for the treatment and study of patients with poliomyelitis so that the best results can be obtained—a pressing problem with the increasing incidence of the disease.

J. W. ALDREN TURNER.

ADVANCES IN MEDICINE

Advances in Internal Medicine. Volume V. Edited by William Dock, M.D., and I. Snapper, M.D. (Pp. 464. £4.) Chicago: Yearbook Publishers. London: Interscience Publishers. 1952.

The average clinical scientist or academically minded consultant tries to skim through at least 30 to 40 weekly, monthly, and quarterly journals to keep *au fait* with what is going on in his subject. It is more difficult to establish a routine for dealing with the annual publications, of which the present is an example, and there are therefore good grounds why they should be reviewed in the same way as books are. Some of these volumes are reprints of courses of lectures and owe their publication merely to local piety or the need to expend an earmarked bequest. Others, however, are of more serious interest, and this one has shown itself to be a useful annual review on whose table of contents the aspiring physician should keep a watchful eye. The present volume of approximately 450 pages contains seven articles, five by American and two by European authors. The lists of references in most of them run up to 150–200 titles. The subjects treated are diseases of the pregnant woman affecting the offspring, catheterization of the heart, portal hypertension, the anaemia of infection, gout, ganglionic and adrenergic blocking agents, influenza, A.C.T.H. and cortisone, and the abnormal proteins in myeloma. The last is an article by Waldenström in which he discusses the whole subject of hyperglobulinaemia. It is an admirable review of a recondite subject which is nevertheless of great interest to haematologists. Most of the other articles are of more general interest. This is indeed an excellent publication, and the only drawback to it is the high price.

L. J. WITTS.

PSYCHOLOGY OF TWINS

Twins: A Study of Three Pairs of Identical Twins. By Dorothy Burlingham. (Pp. 94 and 28 appendices. £1 15s.) London: Imago Publishing Co. 1952.

Mrs. Burlingham's publications with Miss Freud on the work of the Hampstead war nurseries have achieved world-wide recognition. We now have a beautifully produced volume which is a study of three sets of identical twins, and this too will redound to the credit of those who organized the remarkable work done in the war nurseries in London under air attack. The high price of the book must be due to the development charts which are an essential part of it. Mrs. Burlingham has found a method, using three-colour printing, whereby the reader may easily follow the details of the development of each child as a person, and of each child in relation to the development of the twin.

The text is short; it contains well-balanced views on twins and their special problems of emotional development, with the attendant problems of management. Mrs. Burlingham is also able to show that close observation of twins can provide material for work on the theory of the early stages of personality growth.

Children have brothers and sisters, they have animals, real or stuffed or imaginary, they have dolls, they have dream-siblings, fantasies of belonging to a home other than their own, and so on. The problem is, How does a real twin fit in with all these and other similar enrichments and complications that belong to all infants and children? According to Mrs. Burlingham the relationship to the twin is used to soften the crude anxieties that belong to the relation of the child to the parents—that is to say, that belong to the Oedipus complex. But there is also the meaning of twinship to infants who have not yet reached the Oedipus complex level, to those children who have not developed well enough at the earliest stages and who cannot achieve the status of whole persons engaged in inter-personal relationships. There is much work to be done just here, and twins do give a special type of evidence that is useful, and which can, moreover, be collected outside psycho-analysis, by direct observation. For those who are interested in this type of problem the book is probably the most comprehensive work of its kind in existence.

D. W. WINNICOTT.

GYNAECOLOGICAL DIAGNOSIS

Handbook of Gynaecological Diagnosis for Practitioners and Students. By Professor Walter Neuweiler, M.D. Translated from the German by Dr. Paul Ederer. (Pp. 448; 406 figures. £4.) London: William Heinemann Medical Books. 1952.

Dr. Walter Neuweiler is professor of midwifery and gynaecology at the University of Berne, and this is a translation of his *Lehrbuch der gynäkologischen Diagnostik für Ärzte und Studierende.* And an excellent translation it is. The English is impeccable, and the illustrations are not only numerous but are mostly of a high quality. The reproduction of radiographs could hardly be bettered.

The author's thesis is that satisfactory treatment depends on accurate diagnosis, and that the diagnosis demands study of the patient as a whole rather than of her pelvic organs. He concentrates on clinical methods rather than adventitious aids, and the first 100 pages are devoted to a masterly account of history-taking and physical examination. The accounts of colposcopy, hysterosalpingography, endometrial biopsy, and other methods of investigation are short but satisfying.

The major part of the book, however, is rather surprisingly planned on the basis of pathology and follows the usual scheme of setting out in logical order the various morbid processes which may affect each pelvic organ. The clinical features and aetiology of each are discussed separately, but many useful clinical hints and observations can be found. There are also small sections devoted to symptoms such as backache, sterility, discharge, amenorrhoea, and excessive uterine haemorrhage. These, although showing a more clinical approach, do not attain the high standard set elsewhere. One pleasing result of the particular arrangement is that the pathological basis and mechanism of production of clinical features are often explained.

Although all manner of quite rare conditions receive some mention, the work is not intended to be exhaustive or to be an all-purpose textbook. It is designed to supplement rather than to replace standard gynaecological books, and, judged in this light, it is unquestionably attractive.

T. N. A. JEFFCOATE.

During the war Dr. George Spanopoulo, now a general practitioner in Cyprus, served as an R.M.O. with the British Army, and in a little book, *Rabaguena* (Nicosia: Zavallis Press), he describes his experiences from arriving in the middle of the Kalahari Desert to being made a Bechuana chief with the title "Father of Crocodiles." He tells some good stories of the natives of Bechuanaland, their evident enjoyment of castor oil, and the schemes he had to resort to in order to impress them with the powers of his remedies. Indeed, his story has many illustrations of how primitive people prefer the doctor to bring his magic rather than his science to their aid.

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POST-PARTUM HAEMORRHAGE

Post-partum haemorrhage, including third-stage bleeding, is still a leading cause of maternal death. That this should be so despite the advent of the blood bank and of the obstetric flying squad, and at a time when an increasing proportion of deliveries are conducted in hospital, has led in recent years to expressions of dissatisfaction with the traditional methods of management of the third stage of labour. Despite the rearguard action of the old school, championed most recently by Hammond,[1] the trend in institutional midwifery is to discard controlling the fundus, to deprecate Credé's method of placental expression, and to favour the prophylactic intravenous injection of ergometrine towards the close of the second stage. In last week's *British Medical Journal* (p. 643), Drs. J. D. Martin and J. G. Dumoulin added to the literature another report on the efficacy of intravenous ergometrine in shortening the third stage and in preventing post-partum haemorrhage. Secondary relaxation of the uterus may still occur after the delivery of the placenta, but this can be prevented by a further intramuscular injection at this time.[2] In some hospitals prophylactic intravenous ergometrine is given in all labours, but in others it is used only when shortening of the third stage is particularly desired because the risk of bleeding is thought to be greater than average—for instance, when the birth is a multiple one, when there has been a previous history of an abnormal third stage, and when delivery has been performed under general anaesthesia. Prolonged labour is also generally quoted as predisposing to post-partum haemorrhage, but it is surprising how often such bleeding follows a short and efficient labour. One further advantage of delivering the placenta as soon as possible is that it reduces the blood loss from lacerations or episiotomy wounds because these can then be sutured earlier.

Martin and Dumoulin confirm that the timing of the injection of ergometrine with the crowning of the foetal head or the delivery of the anterior shoulder is a most important point of technique. They differ from some, but not all, previous investigators in having found that the procedure caused a significant increase in the rate of manual removal of the placenta. But, even if this point is conceded to them, it is not a serious drawback in hospital practice, where the operation of manual removal is a safe procedure in skilled hands.[3] But this operation does not carry the same freedom from risk in domiciliary practice, in which, therefore, the routine use of prophylactic intravenous ergometrine is not advised. This may seem a serious disadvantage to the general practitioner, but it must be viewed in proper perspective, for factors other than the length of the third stage are concerned in the prevention and treatment of post-partum haemorrhage. Thus, for example, it is of the first importance to keep the haemoglobin of the expectant mother at as high a figure as possible. Skilled conduct of the first stages of labour is reflected in a low rate of traumatic as well as atonic post-partum haemorrhage. In particular the slow delivery of the foetal body encourages normal uterine action in the third stage. Further, Hammond[1] has shown that the proper and efficient management of the third stage along traditional lines has excellent results. Some would modify the classical instructions by substituting a "hands off the uterus" policy for the time-honoured controlling or guarding of the fundus, but with well-trained attendants little if anything is gained thereby. In an obese patient a relaxed uterus distended with blood may be overlooked unless the fundus is controlled.[4] Finally, should the third stage be marked by atony and bleeding, the prompt administration of intravenous ergometrine will cause the uterus to contract, and the placenta can then be delivered or, at worst, the bleeding will be controlled until either the obstetric flying squad answers the summons or preparations are made for manual removal of the placenta.

Once the placenta is delivered the mother should be watched for a further hour. It is in this time that true post-partum haemorrhage is most likely to occur: indeed, there is much to commend the suggestion that this first post-partum hour be designated the fourth stage of labour.[5] If bleeding occurs after the completion of the third stage oxytocic drugs are the first line of treatment, but if the haemorrhage persists or recurs exploration of the uterus should not be deferred. Most commonly clots or retained placental fragments will be found, but it is also necessary to exclude rupture of the uterus and even incomplete

[1] *J. Obstet. Gynaec. Brit. Emp.*, 1952, **59**, 493.
[2] Snaith, L. M., ibid., 1951, **58**, 633.
[3] Cacciarelli, R. A., *Amer. J. Obstet. Gynec.*, 1949, **57**, 351.
[4] Macafee, C. H. G., in *Modern Trends in Obstetrics and Gynaecology*, 1950, London, p. 323.
[5] Greenberg, E. M., *Amer. J. Obstet. Gynec.*, 1946, **52**, 746.

uterine inversion. From the point of view of the mother, perhaps the least fortunate patient is the one who loses a moderate amount of blood—more than normally attends labour but less than warrants transfusion. An unremarked and untreated post-natal anaemia is a serious handicap, lessening the resistance to infection, slowing the rate of recovery from labour, and denying the mother the fullness of energy and well-being necessary for the discharge of her duties and the enjoyment of her baby.

THE HEALTH SERVICE ESTIMATES

A year ago, in commenting on the Health Service estimates, we pointed out that they appeared to have achieved an uneasy stability—which, as it happened, was temporarily upset by the Danckwerts award to general practitioners. Now the budget season has come round again, and the Health Service estimates are being scrutinized to see whether stability has been maintained.

Last year, if the Danckwerts award is ignored, stability was achieved by the imposition of new charges on the patient. Apart from their deterrent effect, the charges for spectacles, dental treatment and dentures, and for drugs were between them estimated to bring in over £23m. in the year now ending. In addition, small sums were to be saved in the hospital service by charges for appliances and drugs for out-patients, and by a higher charge for amenity beds. The effect was to allow the Health Service roughly the same amount of resources at the new prices—which had risen sharply in the preceding twelve months—but to make the patient rather than the taxpayer meet the heavier bill. This year policy seems to have somewhat changed. As a special correspondent shows on page 723, the net cost to the taxpayer has risen to £410m. largely because of the higher payments to general practitioners. There are also increases of varying amounts in the other main items of expenditure. But the charges in the coming year—in the ophthalmic, dental, and pharmaceutical services—are estimated to yield less than £18m. In other words, whereas last year the patient was intended to relieve the taxpayer, this year the taxpayer appears to be shouldering more of the burden.

On Budget Day the Chancellor of the Exchequer may give some information on how effective the charges have been. What is chiefly significant at this stage is that in spite of maintaining the yield from the charges roughly at last year's figure the taxpayer's drugs bill is increased by over £4m. The fall in the total estimated yield from the charges is mainly accounted for by a reduction of £4m. in patients' payments for dental treatment and dentures. In this case, however, the charge seems to have been more effective as a deterrent than the prescriptions charge, for the gross receipts of dentists are estimated to show a further fall—but not enough to save the taxpayer from having to pay a little more for this service as well.

An important feature of this year's estimates is the virtual stability of the grants to hospital boards. Hitherto hospital budgets have been allowed to jump by something like £20m. from year to year, and even then hospital authorities have not been able to undertake much desirable expansion and re-equipment. This year they have not even been able to increase their expenditure to take into account the rise in prices—which has continued in 1952–3, though to a much smaller extent than in the previous twelve months. On the face of it this would imply that the hospitals' budgets have been reduced in real terms, which would in its turn imply a contraction in services. Or it may be that expansion planned a year ago is not being carried out. What does seem to be clear from the estimates is that Health Service expenditure is now marked by a duel between the hospitals and prescriptions. Last year the hospitals were allowed an increase of about £21m. in their budgets, while an attempt was made to keep prescribing in check by means of the shilling charge. This year prescribing has been allowed more latitude, whereas hospital budgets have been rigidly kept down. In fact there are signs that the drugs bill is getting out of control. In the first full year of the Health Service £35m. was spent on drugs prescribed by general practitioners, and this figure was high enough to impel the Labour Government to take power to impose a charge. In the coming year the comparable cost is estimated at nearly £52m., and, even when allowance has been made for the charge, the net cost to the taxpayer is £10m. more than in 1949–50.

The drugs bill is difficult to control because, apart from increasing costs of material year by year, its size depends ultimately on the action of individual general practitioners. It cannot be reduced to any extent by cuts in chemists' fees, for, as the analysis shows, three-fifths of the total is accounted for by the cost of ingredients. Again, many important new drugs are very expensive. Our correspondent points out that in Scotland the pharmaceutical service is estimated to cost less in the coming year than in 1952–3. Yet the price of drugs is the same on each

side of the Border. Perhaps Scottish patients are not so attached to bottles of medicine as the English and Welsh. Or are Scottish doctors more careful in their prescribing ?

POISONS IN AGRICULTURE

Since the Threshing Machine Act of 1878 and the Chaff Cutting Machine Act of 1897 no further legislation had been introduced to safeguard the health of agricultural and horticultural workers until the enactment of the Bill known as the Agriculture (Poisonous Substances) Act, 1952. Regulations under the Act have now been made by the Ministry of Agriculture and Fisheries in England and Wales and the Secretary of State for Scotland. They are for the purpose of protecting employees against risks of poisoning from the dinitro and organophosphorus compounds, which are now extensively used in agriculture and horticulture for the control of weeds and pests.

Because of the food shortage since the war, the search for chemical substances to be used as selective weed-killers and insecticides became intense. Many of these chemical substances are extremely toxic to both man and animals. They were brought into general use before methods of safe handling had been studied, and deaths and cases of acute poisoning occurred in Britain, on the continent of Europe, and in the U.S.A.[1-5]

The dinitro compounds named in the regulations are D.N.C. (dinitro-*ortho*-cresol, or D.N.O.C.) and "dinoseb" (dinitro-*sec*-butyl phenol, or D.N.B.P.). D.N.C. is a selective weed-killer and is widely used in the spring as a spray on cereal crops; dinoseb is mainly used as a spray on leguminous crops. They behave like cumulative drugs in man.[6] The symptoms of acute poisoning are insidious in onset, but, once initiated, progress with extreme rapidity. Death has occurred within one hour of the first signs of illness.[1] The basal metabolism may be raised to above 300% of normal, and death from asphyxia or heat stroke occurs. There is no specific treatment for poisoning by the dinitro compounds.

The organo-phosphorus insecticides named in the regulations are "parathion," "schradan," "dimefox," "mipafox," and T.E.P.P. (H.E.T.P.). These compounds are powerful insecticides and are extremely toxic to both man and animals. Their pharmacological action is that of irreversible inhibition of the cholinesterase enzymes. Reports of cases of poisoning and methods of treatment have been fully described.[2-4]

The regulations prohibit the use of the dinitro and the organo-phosphorus compounds unless the men working with them are wearing protective clothing. The protective clothing varies according to the particular operation carried out, and includes rubber gloves, rubber boots, face-shield, hood, and either overalls or mackintosh. The number of hours during which workers can be employed are restricted to ten hours in any one day and sixty hours during seven days. The employment of any worker under the age of 18 is prohibited. The regulations also contain requirements about the provision and maintenance of protective clothing, the provision of washing facilities for workers, the notification of sickness and absence, the training and supervision of workers, and the keeping of registers.

The regulations serve to emphasize to both worker and employer that these chemicals are highly toxic. They are open to criticism for the reliance they place on the wearing of face-shields rather than full face respirators. The main route of absorption is through the lungs, and face-shields do not prevent absorption by this route during spraying operations. They are likely to be particularly ineffectual when organo-phosphorus compounds are used in an enclosed space such as a greenhouse. The regulations do not make adequate provision for the medical supervision of workers. Since the early symptoms and signs of poisoning are vague and indefinite and do not occur until potentially dangerous quantities of the poisons have been absorbed, routine blood tests on the workers would serve to detect absorption of significant amounts before the onset of symptoms, which are often irreversible. Methods for the measurement of dinitro compounds in small quantities of blood have been developed,[7] as also have methods for estimating the cholinesterase activity on 0.1 ml. of blood.[8]

1 Bidstrup, P. L., and Payne, D. J. H., *British Medical Journal*, 1951, **2**, 16.
2 Report to Pesticides Committee, *J. Amer. med. Ass.*, 1950, **144**, 104.
3 Grob, D., *et al.*, *Bull. Johns Hopk. Hosp.*, 1950, **87**, 106.
4 Abrams, H. K., *et al.*, *J. Amer. med. Ass.*, 1950, **144**, 107.
5 Bidstrup, P. L., *British Medical Journal*, 1950, **2**, 548.
6 Harvey, D. G., *et al.*, ibid., 1951, **2**, 13.
7 Harvey, D. G., *Lancet*, 1952, **1**, 796.
8 Aldridge, W. N., and Davies, D. R., *British Medical Journal*, 1952, **1**, 945.

MORTALITY IN AMPUTEES

Some surprising effects of amputation and sepsis are revealed by a searching investigation, recently completed, into the medical fate of several thousands of Service amputees of the 1914–18 war. In 1950 the Ministry of Pensions appointed a committee of eminent medical men under the chairmanship of Sir Ernest Rock Carling to consider whether amputees are living as long as other people and whether they are more liable to cardiovascular disease. An interim report appeared in 1951, and now a final report has been issued.

The interim findings were as follows. First, living amputees did not seem to be unduly prone to suffer from heart disease or hypertension. Secondly, the mortality rates during 1930–50 of all pensioners who had suffered limb wounds during 1914–18 did not differ much from what was expected, but those who had suffered the more severe wounds and amputations had appreciably higher rates. Thirdly, among the pensioners who died during 1945–9 the average age at death of leg amputees was a little lower, and more of the deaths were due to cardiovascular disease (though not to a statistically significant extent) than among a control group of pensioners who had suffered minor leg wounds only, without amputation. The investigation was subsequently continued in order to explore these divergencies further, to extend the terms of reference to cover certain types of wound, particularly fracture of femur, that did not lead to amputation, and to consider the influence of serious sepsis, overweight, and sedentary life. Little information about the last two factors was forthcoming, but a detailed analysis of the effects of sepsis was carried out.

The full medical records of one-third of the pensioners who had received leg wounds in the 1914–18 war and who had died during 1945–9 were classified into several categories. It was found that men who had had one leg amputated as the result of their 1914–18 service died on the average at a younger age during 1945–9 than those who had sustained a fracture of femur merely, and these in turn died sooner than those who had only a minor wound. But within each of these three classes the pensioners with a history at some time of serious sepsis died younger than those with no such history. Thus the nature and severity of the wound, and, independently, the degree of sepsis associated, both had their effect upon the average longevity of the individuals concerned. It was also found that men who had had both legs amputated, or had had single above-knee amputations, died somewhat younger than those with below-knee amputations or minor wounds only; and that cases classed as serious sepsis on account of osteomyelitis or suppurating joint fared worse than those with necrosis, sequestra, or sinuses allocated to the "serious" sepsis category because of their chronicity. The percentage of deaths at ages under 60 in the main groups analysed can be summarized as follows:

	Double Leg Amputees	Single Leg Amputees	Fractured Femur	Minor Wounds
With serious sepsis ..	78·8	60·8	60·1	52·2
Without serious sepsis	63·5	55·5	45·3	44·0

The causes of death of single leg amputees, fractured femur cases, and those with minor wounds were studied, and this revealed only a small excess of cardiovascular disease among the amputees. But when the various groups were subdivided in accordance with history of serious sepsis it was found that men whose records showed evidence of serious sepsis at some time in the past had a higher proportion of deaths from cardiovascular causes, particularly coronary or myocardial disease. For example, among single leg amputees with serious sepsis almost 32% of the deaths were attributed to coronary or myocardial disease, compared with only 22% among amputees with no record of serious sepsis. And over all the cases studied there were 5.5% more deaths from these cardiac causes among the serious sepsis cases than among the others.

As the analysis of causes of death was based on proportionate death rates, an excess of 5.5% from cardiac causes had to be balanced by a corresponding reduction in deaths from other causes, and we should expect the reduction to be distributed evenly among all of the other causes. But surprisingly it was found that in the serious sepsis group, where the 5.5% excess of coronary and myocardial deaths occurred, the excess was almost completely balanced by a deficit of 5.3% for one other main cause—namely, cancer. These figures prompt the suggestion that in some way serious sepsis had two long-term effects on those who suffered from it—some susceptibility to die from certain forms of cardiac disease and some resistance to the attack of cancer. The committee did not regard the deficit of cancer deaths as bearing on its terms of reference but thought it worthy of separate study. However startling to common sense the demonstration of any causative connexion here would be, the decision that it is worth investigating is a sound one. The figures are not easily argued away. They may be a highly improbable coincidence, for the long-odds bet occasionally comes off. But they seem to be free from obvious fallacies, and the committee had the benefit of an analysis of them by Dr. Logan, chief medical statistician at the General Register Office. All the same, two members of the committee sign a minority report in which they doubt the possibility of serious sepsis having these dual long-term effects. They suggest that the basic classification of the cases according to the degree of sepsis suffered was unreliable and led to unwarrantable conclusions, but they do not explain exactly how the suspected fallacy has come about.

Neither the size nor the content of this report makes for easy reading, consisting as it does mainly of statistical tables with brief factual commentaries, but it records a vast amount of tedious though useful research in what is yet a practically unexplored field. The Ministry of Pensions is to be congratulated on its initiative in sponsoring the investigation. There must be plenty of interesting clinical information in the voluminous case records of this Ministry, and it is to be hoped that further research will follow based upon this exceptional store of carefully compiled material.

BETTER CONTROL OF FOOD INFECTION

Some of the infectious diseases have been made notifiable by Act of Parliament. From time to time others have been added to the list by regulations. In the Public Health (Infectious Diseases) Regulations, 1927, which added malaria, dysentery, acute primary pneumonia, and acute influenzal pneumonia to the list of notifiable diseases, provisions were included for reducing the danger of food-borne enteric fever and dysentery by enabling a local authority to prevent persons with these infections from engaging in the handling of food. It is these latter provisions which are affected by the new Public Health (Infectious Diseases) Regulations, 1953, which supplant the 1927 regulations, the provisions with regard to notification remaining unaffected.

As time passed it became apparent that the valuable precautionary measures provided by the 1927 regulations had two drawbacks which seriously limited their effectiveness. The first of these was the fact that the medical officer of health had to report to his local authority before action could be taken in suspending an infected person from an occupation connected with the handling of food. As speed in such matters is essential, it is a wise provision of the new regulations that a local authority may now authorize the medical officer of health to issue notices requiring persons to stop handling food without making a prior report to the local authority, though he is still required to report the circumstances at the earliest opportunity.

The power to deal with food-handlers who were carriers of enteric fever or dysentery naturally led to the desire for similar powers for use on the far more numerous occasions when food-handlers were found to be harbouring the causative organisms of food-poisoning.

The report of the Catering Trade Working Party of the Ministry of Food in 1951 suggested that consideration should be given to the desirability of amending the Public Health (Infectious Diseases) Regulations, 1927, by extending their scope, so far as was practicable, so that the provisions relating to typhoid and paratyphoid fevers and dysentery should become applicable to salmonella infections, staphylococcal food-poisoning, and other infections which may be spread by food. This advice has been taken into account in the framing of the new regulations. A local authority, or the medical officer of health, may now take action when any food-handler is found to be suffering from, or to be a carrier of, typhoid fever, paratyphoid fever or other salmonella infection, dysentery, or staphylococcal infection likely to cause food-poisoning. Moreover, if a medical officer of health has reason to believe that a food-handler may be a carrier of any of these infections, the local authority may give notice to the manager that a medical examination is necessary, and the manager shall give all reasonable assistance in the matter.

The period between 1927 and the present time has seen the establishment of the Public Health Laboratory Service, and nowadays far more food-poisoning outbreaks are fully investigated bacteriologically than formerly. This fact has led to an increasing demand from medical officers of health for the powers given to them in the new regulations. Their proper use will call for close co-operation with the laboratory, particularly in regard to "staphylococcal infection likely to cause food-poisoning."

TERRAMYCIN

Terramycin is now available in hospitals without restriction as to indications for use, and general practitioners will be able to obtain it from regional distribution centres for the treatment of brucellosis, ornithosis, atypical (virus) pneumonia, lymphogranuloma inguinale, and penicillin-resistant staphylococcal infections. Hospital doctors prescribing it for conditions other than these will need to consider how it may best be used. The ranges of activity of all three newer antibiotics, aureomycin, chloramphenicol, and terramycin, coincide closely. Typhoid fever is exceptional in that only chloramphenicol is useful in treating it. This superiority extends to other intestinal infections by Gram-negative bacilli generally, although in most of these the need for antibiotic treatment is not usually imperative. Other diseases for which these three antibiotics alone are valuable, other forms of chemotherapy being without effect, are comparatively rare or unheard of in Britain or difficult to diagnose. They are the virus infections mentioned above, brucellosis, and the typhus group of fevers. But the newer antibiotics have been extensively used for a variety of bacterial infections when these are, or are assumed to be, resistant to penicillin. Here the clearest indication is a serious and demonstrably penicillin-resistant staphylococcal infection: aureomycin and terramycin are both more active against this organism than chloramphenicol. These antibiotics have also been used, where freely available as in the United States, for treating diseases, such as pneumonia, rather than infections by any particular and identified micro-organism, because their "broad spectrum" covers almost every aetiological possibility. Another indication is a mixed infection, such as peritonitis due to bowel perforation, where they are preferable for the same reason. It needs to be emphasized that, when time and facilities permit, treatment should be based on laboratory tests of bacterial sensitivity. Such tests ought to be made, for instance, in order to direct intelligently the treatment of an infection of the urinary tract.

When there are good reasons for believing that any of these three antibiotics will serve, and choice has to be made among them on other grounds, it will doubtless be borne in mind that chloramphenicol is alone among them in being capable of causing aplasia of the bone marrow. However rare a complication this may be—and, as we pointed out recently,[1] its true incidence remains to be determined—its possible occurrence cannot be ignored when other things are equal. Neither aureomycin nor terramycin has been known to produce this effect, but, of the two, aureomycin is rather more liable to cause the minor toxic manifestations of nausea, vomiting, and diarrhoea.

1. *British Medical Journal*, 1953, **1**, 262.

LEFT HEMICOLECTOMY

In the resection of rectal cancer increasing attention is now being paid to the advantage of dividing the main vascular pedicle as high up as possible. Miles,[1] in his classical description of the combined abdomino-perineal operation, advocated ligation of the inferior mesenteric artery below the point where it gives off its first sigmoid branch. According to the work of Goligher,[2] this level is on the average 1½ in. (3.75 cm.) distal to its point of origin from the aorta, and Grinnell and Hiatt[3] have now suggested that attempts to remove this additional short length of artery (and, more important, its accompanying lymph vessels) may be worth while. These authors found no fewer than 10 lymph nodes in this small area. It is only by increasing, in this way, the upward limit of the lymph-node resection that surgeons will be able to save more patients with disease in the C 2 category—that is, with metastases present in the glands up to the level of the ligation of the blood vessels.[4] When the arterial ligature is placed on the inferior mesenteric artery at its origin the nutrition of the left side of the colon from above is dependent on the left branch of the middle colic. An adequate blood supply from this source can reasonably be expected to a point well down in the sigmoid, always provided care is taken to preserve the marginal vessels. Blood reaches the rectum and anus, however, only along the middle and inferior rectal arteries.

1 *Lancet*, 1908, **2**, 1812.
2 *Brit. J. Surg.*, 1949, **37**, 157.
3 *Surg. Gynec. Obstet.*, 1952, **94**, 526.
4 Gabriel, W. B., Dukes, C., and Bussey, H. J. R., *Brit. J. Surg.*, 1935, **23**, 395
5 *J. Chir., Paris*, 1950, **66**, 37.
6 *Rev. Chir., Paris*, 1951, **70**, 70.
7 Dunphy, J. E., and Broderick, E. G., *Surgery*, 1951, **30**, 106.
8 McKittrick, L. S., *Surg. Gynec. Obstet.*, 1948, **87**, 15.
9 Grinnell, R. S., *Ann. Surg.*, 1950, **131**, 494.
10 *Surg. Gynec. Obstet.*, 1908, **6**, 463.
11 Ault, G. W., Castro, A. F., and Smith, R. S., ibid., 1952, **94**, 223.

When ligation of the inferior mesenteric artery at its origin is undertaken as a step in a combined abdomino-perineal resection, no major technical problem results, since the surgeon requires, above, a length of viable bowel only long enough to allow its delivery in the left iliac fossa as a terminal colostomy. In general, however, the higher the cancer is situated in the rectum the stronger must be the argument for high ligation of the main vascular pedicle. In Britain, at least, anterior resection with restoration of continuity is allowable only when the tumour is clearly above the level of the peritoneal reflection, and it would seem to be in the conduct of such an operation that division of the inferior mesenteric artery at its origin would have especial merit. But it is in just such an operation that the surgeon may have a not unnatural reluctance to take this step, since he fears that he may not then be left with a length of bowel which he can easily and safely bring down for suture to the rectal stump—a segment of bowel about the vascularity of which he has in any event already some misgivings. Toupet,[5,6] however, has shown that in most cases a 35-cm. length of bowel can be fashioned (based on the middle colic artery) in such a way that its open end can be brought down even as far as the anus. But to achieve this it is necessary to mobilize not only the descending colon but to free the splenic flexure and the left half of the transverse colon as well. Although this must add considerably to the technical difficulties and to the hazard of the operation, Grinnell[3] has shown that it can be practised with an encouragingly low mortality and morbidity. The same arguments can be used with even more conviction to support proximal division of the inferior mesenteric artery when the carcinoma is situated just above the rectum; and already it is the common, if somewhat paradoxical, practice of many surgeons to carry out anterior resection of the rectum most often for tumours which are really in the lower sigmoid.[7-9]

The logical extension of this wider removal of the lymph-node-bearing tissue would seem to be as a step in the excision of tumours not only in the lower sigmoid but at any site in the left side of the colon even as far as the splenic flexure. It is interesting to recall that sacrifice of the entire inferior mesenteric artery caused not the least alarm to Moynihan,[10] who recognized the importance of the node so constantly situated close to its point of origin and who advocated its ligation at this level for a cancer in the sigmoid flexure. The generally less satisfactory end-results of resection of cancer of the left than of the right side of the colon is no doubt related in some measure to the more complete hemicolectomy which is routinely practised for cancer in the right side of the colon. The limited wedge excisions of the mesentery, so commonly practised for the removal of cancer in the left side of the colon, should no longer be sanctioned.

Although extensive studies of the disposition of the blood supply of the distal colon from the inferior mesenteric artery have been made, more attention could profitably be directed to the length of rectum nourished from below.[11] If anatomical dissection, injection experiments, and experience at operation all suggest that the inferior and middle rectal arteries are adequate to permit a safe anastomosis above the level of the peritoneal reflection, there would be all the more to commend as the standard operation for cancer at this site a left hemicolectomy, to match that already routinely practised with a greater measure of success on the opposite side.

FELLOWS OF THE ROYAL SOCIETY

Four medical men are among the twenty-five new Fellows of the Royal Society elected last week—Professors Henry Barcroft, G. W. Harris, Lionel Penrose, and David Whitteridge. And some distinguished biologists and chemists among the other new Fellows have made notable contributions to the advancement of medicine.

Professor Barcroft, who holds a London University chair of physiology at St. Thomas's Hospital, has conducted many penetrating studies of the vascular system, the blood pressure, and the blood supply of muscles. Before going to St. Thomas's in 1948 he was at Queen's University, Belfast, for some years, holding the Dunville chair of physiology. Professor Harris has recently become Fitzmary professor of physiology at the Institute of Psychiatry, London. He has achieved distinction for his work on the frontiers between neurology and endocrinology, in particular the control of the pituitary by the nervous system—a subject he reviewed in two lectures that were published[1] in this *Journal* just over a year ago. Dr. Penrose equipped himself with a degree in psychology at Cambridge and a year's study in the psychology department of Vienna University before turning to medicine to become an outstanding authority on the genetics of mental deficiency. Now Galton professor of eugenics in London University, he is the author of many papers on divers aspects of human inheritance. Professor Whitteridge, who went to the chair of physiology at Edinburgh two years ago, worked on the physiological effects of blast during the war and has devoted special attention to the investigation of nervous impulses.

Among the non-medical men to be elected F.R.S. are two whose studies have been concerned with chemotherapeutic and antibiotic agents. Dr. J. W. Cornforth, a chemist at the National Institute for Medical Research, worked with the Oxford team on the synthesis of penicillin and related compounds. Dr. E. F. Gale is director of a Medical Research Council unit for chemical microbiology at Cambridge, and is distinguished especially for his work on the effect of penicillin and other chemotherapeutic agents on the amino-acid metabolism of bacteria. Also at Cambridge is Dr. K. Bailey, who is assistant director of research at the biochemistry laboratory there. His work has chiefly been on the chemistry of proteins, including insulin. Lord Rothschild's work on the physiology of reproduction has brought outstanding advances in our knowledge of fertilization, particularly in animals but to some extent in man also. He has been chairman of the Agricultural Research Council since 1946.

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1 *British Medical Journal*, 1951, **2**, 559.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

RECURRENT BOILS

BY

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A boil, or furuncle, is a localized staphylococcal infection of a skin appendage, usually a pilo-sebaceous follicle or a sweat gland. An abscess occurs with central necrosis, followed after a few days by discharge of pus and sloughing of the follicle or gland. Healing is usually rapid. In a carbuncle many skin appendages are infected and the inflammation spreads more deeply, affecting the subcutaneous tissues. A local crop of boils results from infection of near-by follicles, but with widespread boils we have a contagious disease affecting any part of the skin surface. The staphylococcus causing these infections is ubiquitous and can be found in the noses of half of the adult population and on the skin of a quarter of them.

Except as regards local treatment, the problem of recurrent boils is much the same whether the affection is generalized or localized to one area, such as the neck or axilla. The problem has serious and important facets. The presence of boils means a high population of virulent staphylococci over the whole skin of the patient, who then becomes a danger to himself and others, indeed to the community. It is a general medical problem in its widest sense, but the possibility of a septic focus in the patient and the reasons for his lowered resistance must be investigated. There is also the question of the indication for chemotherapy and antibiotics, which on the face of it would seem to be the specific line of treatment.

Resistance to Infection

The skin forms an efficient barrier to infection, and when its surface is unbroken it can be penetrated by bacteria only through the openings of follicles and glands. The acidity of the secretions and the keratin layer provides an "acid mantle" which controls the bacterial flora on the skin surface. Once organisms have penetrated the skin the humoral and cellular resistance of the body provides further protection; the development of specific immunity is stimulated.

Friction reduces locally the resistance of the skin to infection. Thus rowers using fixed seats and riders who are inexperienced get boils on the buttocks; rough sleeves or collars may provoke boils on wrists or neck; scratching from pruritus ani may be associated with recurrent boils on the perineum. It is as well to think of scabies when there are multiple boils on the buttocks. But any itching skin disease, whether it be eczema, urticaria, pediculosis, or some other, may be complicated by boils, as may any general disease associated with itching (jaundice, Hodgkin's disease, leukaemia, etc.).

The resistance of the skin to infection is reduced by moisture and excessive oiliness, because these disturb the acid mantle. The moist, greasy skin of the seborrhoeic subject is particularly prone to infection, and maceration of the skin brought about by profuse sweating, wet occupations, and moist applications lowers its resistance. "Salt-water boils" are seen on the wrists of sailors and fishermen whose skin, wet with sea-water, is chafed by the stiff cuffs of their oilskins. When work requires prolonged contact of the skin with cutting oils, lubricants, greases, and waxes, oil acne and boils may appear, especially on the hairy parts such as the forearms and thighs. Tar workers often suffer with recurrent boils. Alkalis which are keratolytic and neutralize the acid mantle also lower the skin's resistance.

The presence of a boil leads to an enormous increase in the bacterial population of the skin, and infection of other pilo-sebaceous follicles becomes more likely. The population is also increased when there is dental or nasal sinus infection or when other septic foci are present. The old dictum should be remembered: look in the mouth, nose, and throat whenever there is skin sepsis. It has been shown that with tinea pedis there is a local increase in the number of staphylococci, and a general increase may follow contact with another individual suffering from boils.

More important, probably, than the organisms on the skin surface is a lowering of general resistance to infection. In an annotation on pyococcal dermatoses (*British Medical Journal*, 1949, **1**, 858) it was stated that a psychogenic, endocrine, nutritional, or toxic influence plays a major part in these conditions. This would seem to be true, and the order in which they are placed should be noted.

In many patients with recurrent boils the condition appears during a period of mental strain or emotional distress. The lowering of resistance to infection in this way need cause no surprise and it is generally appreciated by the lay public. In plague epidemics in times past it was recognized that those most fearful of infection were the most likely to fall victims. Endocrine influences play a part which is not well understood, but the frequency of boils in adolescence seems related to the increased activity of the sebaceous glands from hormonal stimulation. Some people are particularly predisposed to boils, which appear as their reaction to stress of any kind. The reason for this is not known, but is probably associated with endocrine disturbances.

Lowering of the resistance of the skin to infection is associated more often with malnutrition than undernutrition, and particularly with excessive carbohydrate intake. Any disorder of metabolism may lower resistance, but patients with diabetes mellitus are thought, though on no very firm evidence, to be especially prone to skin infection. Whether or not this be true, the diagnosis of diabetes mellitus in a patient with skin infection is of the utmost importance because of the greater insulin requirement and the danger of coma. The urine of a patient with boils must always be examined—it may lead to the discovery of diabetes, perhaps previously unsuspected. However, boils and carbuncles may produce a transient toxic glycosuria which is of no importance. Other general debilitating conditions, such as jaundice, anaemia, nephritis, and tuberculosis, also reduce the resistance of the skin to infection.

Complications

Complications have been less common since the advent of chemotherapy and the antibiotics. Mild debility and local complications such as lymphangitis and lymphadenitis are common, but staphylococcal septicaemia or septic embolism causing carbuncle of the kidney and perinephric abscess, osteomyelitis, or cerebral abscess are not often encountered. It is well known that thrombosis of the intracranial venous sinuses may complicate boils on the head, especially on the face, by direct extension. It is less generally appreciated

that it may occur with boils on any part of the body as a result of a septic embolism. If cooks or others who touch food have boils, outbreaks of food-poisoning may occur. The precipitation of coma in a diabetic with boils or carbuncles has already been mentioned.

Diagnosis

In the diagnosis of recurrent boils there is little difficulty except to determine the cause, and this requires a full assessment of the underlying factors. Unless a careful history is taken and the patient is examined fully a blunder will occasionally be made. A bromide eruption with small papulo-pustules developing into sterile boils, pustular ringworm (kerion) with discrete lesions, papulo-pustular syphilide, and papulo-pustular tuberculide may all be mistaken for boils if care is not taken. Cutaneous anthrax, which is seen occasionally in this country in leather workers or others who handle hides, might be mistaken for a single boil but not for recurrent ones. A papule, rapidly becoming a pustule, appears usually on an exposed area of skin. There is intense local inflammation, necrosis of the pustule follows with the formation of a black slough, and secondary vesicles soon form around it.

General Treatment

The treatment of widespread boils clearly demands general measures, but even in grouped or localized boils these must not be neglected. The treatment of any patient with recurrent boils must be considered as a general medical problem and the underlying factors dealt with. We must think in terms of focal sepsis and the resistance of the patient to infection. Chemotherapy and the antibiotic drugs provide specific therapy and are most impressive in the treatment of boils. Those occurring on the face should always be treated in this way. Unfortunately, in suppressing the staphylococcus so effectively they do not allow the process of active immunity to be developed, and a relapse often follows cessation of treatment. Care must be taken that concentration on local treatment combined with injections of penicillin does not lead to neglect of the cause of the problem.

Whether the boils are localized in groups or whether they are widespread, the possibility of focal sepsis should be considered. Infection of the teeth, nose, nasal sinuses, or throat must receive appropriate treatment. Tinea pedis must not be neglected.

Whenever emotional or mental strain plays a part rest will be required, possibly a holiday from work or away from home. Mild sedation is helpful in such patients, and phenobarbitone, ¼ gr. (16 mg.) twice daily by mouth, may usefully be given.

The question of employment must be considered. The seborrhoeic type of individual tolerates heat and moisture badly, and skin sepsis is common in miners of this type who work under such conditions. After greasy work the skin should be washed thoroughly with soap and water. Sponging with cetrimide as a 1% solution in water removes grease and dirt from the skin and is actively bactericidal. It is inactive in the presence of soap and occasionally irritates the skin, but otherwise is helpful if the patient can be persuaded to go to the trouble of using it.

A balanced diet is important. Sweet cakes, suet puddings, fried potatoes, and other carbohydrates should be eaten in moderation. Chocolate is best avoided. Sugar in tea and coffee may be replaced by saccharin. Citrus fruits and fresh vegetables may be eaten in abundance. Additional vitamin-B complex is helpful. Yeast is not of much value unless it is fresh and taken in large quantities. Patients with boils are sometimes anaemic, and iron may be given—for example, one or two ferrous sulphate tablets three times a day after meals.

Active immunization by an autogenous staphylococcal vaccine or staphylococcus toxoid is found to be effective by some physicians, toxoid appearing to be the better. It is as well to start a course when there are no active boils. A combination of toxoid and a stock vaccine such as "vaccoid" may be used, 0.1 ml. of the weak preparation being enough for the first dose. The material is injected intradermally and the dose increased by 0.1 ml. each week until 0.5 ml. is reached, when the stronger preparation, containing five times the quantity of toxoid, may be used in a similar manner, beginning once more with a dose of 0.1 ml. Reactions, general or local, are to be avoided, and if such occur the dose for the following injection should not be increased.

If boils do not stimulate the production of active immunity it seems unlikely that vaccines will do so unless they provide a stronger stimulus, whether specific or non-specific. Some authorities believe the action of vaccines and toxoid to be one of desensitization to the staphylococcus and its toxins. However, treatment with vaccines or toxoid, or with manganese or tin, does not provide a cure, and, like antibiotic therapy, will prove disappointing unless the essential cause is found and treated.

Local Treatment

The principles of local treatment are rest, dry heat, and the minimum of interference. Because it is important to prevent, if possible, the infection of other follicles, the surrounding skin should be kept healthy and as sterile as practicable. The skin around a boil should be swabbed with spirit or brilliant green paint (perchloride of mercury 0.5%, brilliant green 0.5%, industrial spirit 99%). The topical application of antibiotics is only of temporary value, and may lead to sensitization of the skin. Hot fomentations and bread or kaolin poultices should be avoided, as these may burn the skin and certainly make it sodden and more liable to infection. Adhesive plaster dressings also make the skin unhealthy. Dry heat is useful; an infra-red lamp or an old-fashioned electric radiator or even a hot-water bottle over dry dressings may be employed. Short-wave diathermy, if available, is helpful. Local fractional doses of superficial *x* rays seem to abort the condition in the early stage and to prevent crops of boils appearing in the area treated.

The squeezing of boils is best avoided. Surgery has little place in the treatment, but when a boil becomes fluctuant, and not before, it may be incised. Large cruciate incisions and packing are quite unnecessary and do more harm than good. A dry dressing to absorb the pus may be applied and changed frequently, though if preferred magnesium sulphate paste may be used.

Widespread Boils

Once a boil has burst there is a great increase in the bacterial population of the skin near by and over the body as a whole. With lowered resistance this may result in recurrent widespread boils, and the condition must be treated as a contagious disease in which there is superficial external infection and reinfection. Every precaution possible to prevent the continuation of autogenous reinoculation must be taken. The bacterial increase can be controlled to some extent by bathing in or sponging with 1% solution of cetrimide or with 1 in 4,000 potassium permanganate. The permanganate must be dissolved in a little water before addition to the bath, as contact of a crystal with the skin may cause burning. Potassium permanganate discolours the bath, which is cleaned with difficulty, though the brownish stain can be removed with vinegar, oxalic acid, or some of the abrasive cleansers. Antiseptic soaps may be preferred, but they do not have the toughening and tanning effect of permanganate, and they may neutralize the acid mantle. After such antiseptic baths a dusting powder

containing 10% of calomel in zinc oxide is especially useful with widespread furunculosis, provided the patient is not sensitive to mercury. Cotton underclothes, changed daily, should be worn, as they can be boiled. Soiled dressings must not be allowed to touch skin areas which have not been protected by disinfectant solutions, and the hands of the patient and those attending him should be kept scrupulously clean.

The bacterial population of the skin remains high for weeks after a boil has healed, and these efforts to reduce the staphylococcal flora must be continued for some time. The nose of the patient is likely to be harbouring numerous virulent staphylococci, although physical signs are absent. Careful cleansing of the nasal vestibule with soap and water several times a day or a thin smear of ammoniated mercury 10 gr. (0.65 g.) in hydrous ointment 1 oz. (30 g.) reduces the danger from this source. In the presence of sinus infection this measure is, of course, purely palliative, and, as mentioned before, treatment of the nose and sinuses may be required.

Grouped Recurrent Boils

Hidradenitis suppurativa is an example of recurrent boils appearing as a local condition. The apocrine sweat glands develop at the time of puberty in the axillae, on the nipples, and in the region of the anus and genitals. They are subcutaneous and their ducts usually open into hair follicles.

A troublesome inflammation of these glands occurs occasionally and is more common in women. One or both axillae may be affected, and sometimes the perineum and groins. In these areas recurrent abscesses may result. A tender subcutaneous swelling appears, with redness of the overlying skin. Although it may settle down without suppuration, it often becomes fluctuant and discharges pus after bursting. Other glands become infected, and the condition may continue for weeks with great discomfort. Irregular scarring with cheloid formation may result.

It is probable that there is sweat retention followed by secondary infection. Although psychological and endocrine factors play an important part, mechanical causes may be present, such as maceration of the skin from sweat, especially when rubber dress protectors are worn. Damage to the duct openings by deodorant applications or depilatories may be a cause.

As with skin infection elsewhere, the cause of the breakdown of the patient's resistance must be determined. Antibiotics are only helpful temporarily, because a relapse often occurs when their use is stopped. The application of brilliant green paint (see above) to the whole of the axilla or other affected area, together with irradiation by *x* rays in a few fractional doses at intervals, will usually clear the disease rapidly, provided general causes are not neglected. As with other boils, fomentations are best avoided and dry heat should be applied. Short-wave diathermy is helpful. Incision may have to be considered, but it is wise to be conservative in order to avoid scarring and cheloid formation. Many of the swellings settle with treatment, and incision is justified only if there is marked fluctuation over an abscess. Full consideration of the treatment, which may involve endocrine therapy or even excision and grafting, is outside the scope of this article.

Conclusion

The objectives in the treatment of recurrent boils should be to keep the skin dry, clean, and free from irritation, to eradicate foci of infection, and to raise the general resistance of the patient.

Next Refresher Course Article.—" Prolapse," by Mr. A. J. Wrigley.

HEALTH SERVICE COSTS

[FROM A SPECIAL CORRESPONDENT]

A year ago, Mr. Crookshank, then Minister of Health, was being hard put to it to maintain the £400m. limit on the Budget's share of Health Service expenditure set by Labour Chancellors of the Exchequer. He could do it, in fact, only by imposing the charges on drugs, appliances, and dental treatment authorized by last year's National Health Service Act. But no sooner had his Health Service estimates been published in full than the Danckwerts award to general practitioners knocked the limit for six, mainly because of the back payments involved. This year's estimates are freed from this complication of back payments, but the effect of the award on the limit is clearly seen in the following table :

*Health Service Estimates**

	£m.			
		1952–3		
Total Net Cost to Taxpayer	1951–2 **398**	Original **392**	Revised **429**	1953–4 **410**
Grants to local health authorities	18·6	20·6	21·2	21·6
General-practitioner service	48·4	48·5	86·9	58·2
Pharmaceutical service† ..	43·6	39·9	40·9	45·0
Dental service†	36·2	20·1	20·4	22·0
Supplementary ophthalmic service†	14·6	6·3	6·3	6·4
Grants to hospital boards ..	274·3	295·6	296·0	297·1
Of which maintenance ..	*260·8*	*285·7*	*286·1*	*287·0*

* Excluding civil defence. † Allowing for charges to patients.

Thus, compared with the pre-Danckwerts estimate, the total net cost of the Health Service to the taxpayer has risen by £18m. Of this, more than half is accounted for by the higher payments to general practitioners resulting from the award; but there are also small and, in one case at least, ominous increases in the other main items of expenditure.

*Expenditure of Local Health Authorities**

	£m.		
	1951–2	1952–3	1953–4
Health centres	†	†	†
Care of mothers and young children	9·4	9·6	9·5
Midwifery	5·0	5·4	5·1
Health visiting	2·7	3·1	3·2
Home nursing	4·3	5·4	5·5
Vaccination and immunization ..	0·5	0·6	0·6
Ambulance service‡	7·9	9·3	9·7
Prevention of illness and aftercare	1·7	2·1	2·2
Home helps	3·5	4·3	4·7
Mental health	1·8	2·1	2·2
Miscellaneous	0·2	0·3	0·3
	37·0	42·2	43·0

* Including estimated expenditure from rates.
† Less than £100,000 in England and Wales.
‡ England and Wales only.

Expenditure on the services of the local health authorities has virtually been stabilized. Indeed, it is impossible to see how it could be otherwise. The initiative in this branch of expenditure comes from the local authorities, and about half the total cost falls on the ratepayer. Already local authorities have had to raise their rates for the coming year—increases of as much as 2s. in the pound are common. They may well hesitate before expanding further any of their health services. And the argument that by so doing they might relieve the hospitals, and therefore the taxpayer, will, not unnaturally, carry no weight. Estimated expenditure on health centres in England and Wales is falling from £94,000 to £50,000, which must mean a virtual cessation of new centres. In Scotland, on the other hand, where the cost of health centres is borne on the executive councils' vote, although the original

estimate for 1952–3 was scaled down from just over £100,000 to £70,000, in 1953–4 an increase to £85,000 is budgeted for.

The effect of the Danckwerts award on the cost of the general-practitioner service has already been referred to. In terms of allocation of financial resources it means that family doctors now receive 12% of central Health Service funds, compared with 10% two years ago. There can be few people who would regard this proportion as too high.

The Pharmaceutical Service

There can be few people, too, who are undisturbed by the continued rise in the cost of the pharmaceutical service. A year ago the Minister of Health stated that it was running at more than £50m. a year. Through the shilling charge he hoped to bring the gross cost down to £47½m.—as a result of the deterrent effect of the charge—and to save another £7½m. by the payments made by those who were not deterred. This would bring the net cost down to £40m. As it turned out, the gross and net cost were put a little higher. But it is now known that the charge has not yielded so much as was expected. Recently Mr. Macleod, the Minister of Health, said that because of the fog and influenza the number of prescriptions issued in 1952–3 would not be less than in the previous year. It is therefore surprising that the yield from the charges has not risen *pro tanto*. According to Mr. Macleod, it was originally estimated that in England and Wales alone in a full year £6.8m. would be saved by patients' payments and £3.9m. by a reduction in the number of prescriptions. This would make a total saving of about £9m. in the ten months for which the charge was in force. But the total saving is in fact now estimated at only £5m. paid by patients. In the circumstances it is a little surprising that the reduction in the estimated yield from the charges in the coming year is not greater than it is.

Cost of Pharmaceutical Service

	£m.		
	1951–2	1952–3	1953–4
(a) Payments to pharmacists:			
Dispensing fees and rota payments	13·6	13·1	12·7
Cost of ingredients and allowance for containers	24·5	27·2	29·9
Allowance for overheads and profits	3·6	6·5	7·2
(b) Payments to doctors and dentists for drugs supplied:	1·9	1·5	1·9
Total gross cost	43·6	48·2	51·7
Patients' payments	—	7·3	6·7
Net cost	43 6	40·9	45 0

An interesting feature of the estimates is that the whole of the increase in costs is accounted for by the service in England and Wales. In Scotland, the total gross cost and the cost of ingredients are put at a lower figure than a year ago, and patients' payments are estimated to be slightly higher, so that there is a saving of about £500,000 in the net cost.

The Dental Service

The effect of the charge for treatment on the cost of the dental service is also interesting. The significance of these figures is that the charge for dental treatment is evidently still acting as a deterrent, as was expected, and because of this the estimated gross receipts of dentists show a further fall for the coming financial year. But the estimated receipts from the charges were evidently wide of the mark a year ago, and have accordingly been greatly reduced for 1953–4. The net effect is a rise of £1.6m. in the cost of the dental service—with Scotland again managing to show a small reduction. But the proportion of the total cost of the Health Service taken by the dental service is down from nearly 10% in 1950–1, the year before the charge for dentures was introduced, to less than 5% in 1953–4.

Dental Service

	£m.		
	1951–2	1952–3	1953–4
Gross receipts of dentists	41·0	31·2	28·8
Payments by patients	4·8*	10·8	6·8
Net cost of service	36·2	20·4	22·0

* For dentures only.

The Hospital Service

By contrast the hospital service now accounts for a much larger share of Health Service costs (61%) than was originally contemplated. What is significant about the new estimates is that for the first time there has been virtually no rise in the estimated grants to hospital boards. Such rise as is shown is, in fact, mainly accounted for by Scottish hospitals. The teaching hospitals in England are actually to have a cut of over £1m. in their grants for maintenance.

The following Table compares the estimated expenditure on the main items of the running costs of hospitals in England and Wales :

Gross Hospital Maintenance Expenditure

	£m.		
	1951–2	1952–3	1953–4
Medical salaries (including specialists)	26·9	31·5	28·8
Nursing salaries	55·5	60·7	59·1
Other salaries and wages	62·7	71·7	76·0
Provisions	25·9	29·1	30·4
Drugs and dressings	9·4	10·4	11·3
Medical and surgical appliances	7·0	8·1	6·7
Fuel, light, and power	11·2	13·9	14·6
Maintenance of buildings	10·3	10·1	8·8
All other	31·9	33·5	33·4
Total	240·8	269·0	269·1

The interesting feature of this Table is the estimated fall in medical and nursing salaries in the coming financial year —the more interesting in view of the higher salaries recently granted to nurses, which were expected to cost £5m. in a full year. The fall may be connected with the freezing of hospital establishments, which has prevented hospital authorities from carrying out expansions planned a year ago. Whatever the reason, it evidently does not apply to Scottish hospitals, whose estimates show no such cut in medical and nursing establishments.

For the first time the Health Service estimates include a forecast of the numbers of staff to be employed by hospital authorities at the beginning of the financial year. They are given in the following Table :

Estimated Hospital Staff on April 1, 1953*

	England and Wales	Scotland†
Consultants	5,300	1,250
Other doctors and dentists	12,000	1,250
Nurses and midwives	148,000	21,400
Administrative and clerical staff	28,000	3,200
Other professional and technical staff; maintenance staff and tradesmen and craftsmen, including transport staff; all other staff	188,000	22,250
	381,300	49,350

* Including the approximate whole-time equivalent of part-time staff.
† Estimated averages for 1953–4.

This Table shows another difference between England and Wales and Scotland. South of the Border, only 30% of total medical and dental staffs are consultants. In Scotland consultants account for half the total.

COLLEGE OF GENERAL PRACTITIONERS

REGIONAL FACULTIES

It is proposed that the peripheral activities of the College shall be organized by a number of Regional Faculties.

Headquarters

Ideally the headquarters of these Regional Faculties should be situated near the offices of the undergraduate and postgraduate deans or directors of the medical schools and the university research departments, for educational purposes and to facilitate arrangements for postgraduate study and research. But in some places this may not be possible; or headquarters may be offered to the College elsewhere, as has already occurred in Birmingham and in Edinburgh. It is felt that a close link like this with the universities will underline the *academic* nature of the College's work.

In London the Director of the Postgraduate Medical Federation of the University of London has generously offered the College accommodation at his headquarters—2, Gordon Square, W.C.1. This arrangement will lead to close co-operation between the two bodies, and should be of considerable benefit both to general practitioners and to those organizing their postgraduate courses. It is hoped that similar co-operation may be arranged between the College's regional faculties and the postgraduate deans or directors of other university cities.

There are 19 universities with medical schools in the British Isles and Republic of Eire—Aberdeen, Belfast, Birmingham, Bristol, Cambridge, Cardiff, Cork, Dublin, Durham, Edinburgh, Galway, Glasgow, Leeds, Liverpool, London, Manchester, Oxford, Sheffield, and St. Andrews. Pilot faculties will be formed at once in London, Birmingham, Bristol, Cardiff, Edinburgh, Belfast, and Dublin. After the first annual general meeting, to be held in the autumn, a further 12 or more regional faculties may be set up in the British Isles: plans for these will be made soon. In areas far away from these university cities faculties may be needed in a few cities or towns that have no medical school (e.g., Plymouth and Inverness). Other regional faculties may be developed in parts of the Commonwealth. Further details will be published next month.

The Foundation Council has approved the establishment of a "Council of the College in Scotland" to co-ordinate the regional faculties and other local organizations in Scotland, and to maintain liaison with the council of the College. It is proposed to open an office in Edinburgh at once.

A meeting of general practitioners in Eire, held in Dublin on March 15, 1953, decided to form a Faculty of the College in Dublin; and an interim committee was set up to study this. Dr. John Fleetwood, of Dublin (chairman of this interim committee), has been elected to the Foundation Council of the College in London.

A meeting of the full Foundation Council, held in London on March 18, 1953, agreed that the College provisional by-law 1 (B) should be altered to read: "A 'registered medical practitioner' means a person holding a medical qualification which has been registered with the General Medical Council or with the equivalent organization of a country or State within the British Commonwealth of Nations and the Republic of Eire."

Status

The status of all Regional Faculties will be equal. For those in Scotland, Wales, Northern Ireland, and Eire it must be clearly understood that they will be free to form colleges of their own in the future if they wish to do so.

Duties

In general the duties of these Regional Faculties will be to relieve the central College council of local responsibilities connected with the activities of the College in the regions concerned. For the first few years the main concern of the faculties will be to help (1) in the teaching of certain aspects of general practice to final-year students and those newly qualified, (2) in the postgraduate education of general practitioners in the region, and (3) in research in general practice. Later, many other functions of the College may devolve upon the Regional Faculties. Members of the board of each faculty will work in close liaison with the local medical school, the postgraduate departments of the university, and the university research departments, the local medical committees of the Ministry of Health, the local Divisions of the B.M.A., and the local medical societies.

Boards of the Regional Faculties

Each board will have up to 21 members—chairman (who may be a member of the College council or co-opted to the council), deputy chairman, member for undergraduate instruction, member for postgraduate study, research member, and honorary secretary. The secretary will keep in touch with members and associates of the College who work in the region, receiving information from them and providing them with information, so that the College and its regional faculty can give them all possible help in the academic field. There will be up to 15 other members, including two associates; and the boards will have power to co-opt further members from the university and elsewhere.

Members of the boards of the Faculties will be elected annually by the members of the College who live in each region. The officers will be elected by the boards themselves.

Meetings of the boards will take place about once a month. Five will be a quorum.

Copies of the minutes of the meetings of the boards will be sent to the College headquarters in London for filing and reference. Each year an annual report from each board will be sent to the College headquarters and incorporated in the College's annual report.

Subcommittees on undergraduate education, postgraduate education, research, etc., will be elected by the boards at any time for special purposes. These subcommittees will have power to co-opt members from the university departments concerned.

The secretarial expenses of the boards will be met by the College.

Will members or associates who care to make further suggestions or comments on the development of these regional faculties please write to the Secretary, The College of General Practitioners, 14, Black Friars Lane, Queen Victoria Street, London, E.C.4.

MATERNITY GRANTS

Over a year ago the National Insurance Advisory Committee (chairman, Sir Will Spens) recommended changes in maternity insurance benefits (*Supplement*, January 26, 1952, p. 28). A Government Bill—National Insurance Bill, 1953—has now been published giving effect to nearly all the recommendations of the advisory committee. A woman confined at home is to get a lump-sum grant of £12, and a woman confined in hospital a grant of £9 (both grants including an attendance allowance of £1 a week for four weeks). The arrangements for paying maternity allowances to women in employment are to be changed. At present a grant of 36s. a week is paid for 13 weeks beginning with the sixth week before the expected date of confinement, making £27 8s. in all when the maternity grant of £4 is added. The Bill increases the grant from £4 to the standard amount of £9 (or, when the confinement takes place at home, £12), and the maternity allowance, reduced from 36s. to 32s. 6d. a week, is to be paid for eighteen weeks, starting eleven weeks before the expected date of confinement. These

changes have the effect of increasing the total amount paid from £27 8s. to £38 5s., or in the case of home confinement to £41 5s. It is estimated that these proposals will cost an additional £2,500,000 a year.

Nova et Vetera

THE FIRST GREAT AMERICAN PHYSICIAN

Letters of Benjamin Rush. Edited by L. H. Butterfield. Published for the American Philosophical Society by Princeton University Press, 1951. Vol. I: 1761–1792, pp. lxxxvii+624. Vol. II: 1793–1813, pp. 625–1,295. Price for 2 vols. 97s. 6d. London: Geoffrey Cumberlege. 1951.

Benjamin Rush (1745–1813), of Pennsylvania, a signer of the American Declaration of Independence, was a figure highly characteristic of his time and circumstances. He was a graduate of Princeton and Edinburgh. At the latter university he had as teachers Cullen, Black, and Alexander Monro Secundus. In his own country he came to occupy a very important position both in politics and in the medical profession. He introduced clinical instruction in the Pennsylvania Hospital, to which he was physician for 30 years (1783–1813), and he was for long also Treasurer of the United States Mint (1799–1813). Despite these avocations he found time for some excellent first-hand research describing cholera infantum in 1773 and dengue in 1780, writing a first-class account of the Philadelphia yellow-fever epidemic in 1793, giving the first account of the diseases of American Indians in 1774 and 1798, and issuing a work on the hygiene of troops in 1777. He was a strong advocate of temperance, and emphasized the importance of diet and the necessity to health of the extraction of decayed teeth. He wrote and spoke freely on non-medical subjects, was a vigorous and magnetic personality, and had a full, balanced, and active mind. He left an autobiography which was edited in 1948 for the American Philosophical Society by Professor G. W. Corner.

Rush's vivid personality is much involved in his immediate environment. He was essentially a townsman and a Philadelphian, for he never took a holiday, and after his return to America he seldom left Philadelphia, and almost never by choice. In his *Autobiography* he says that he "by no means depended exclusively on books. I made, as far as was in my power, every person I conversed with contribute to my improvement." His correspondence was immense, and no American, and few English, writers furnish so many and such excellent pictures of city life in his era. As a writer he was studiously clear, and this induced many to elicit his views on a multitude of topics. His correspondence deals with subjects as diverse as psychiatry and forestry, veterinary science and ventilation of ships, the study of punishments and of chemistry, the training of children, the liberation of the Spanish colonies, university curricula, and how a stepmother should comport herself. On almost any subject Rush was glad to give an opinion. Despite the positiveness of his opinions he remained on terms of intimate friendship with men of the most diverse views. The collection of letters in these two large volumes is thus a record of the many amiable traits in Rush's character which his deadly earnestness and his contentiousness have hitherto often obscured. Rush was essentially a communicative man, and his abundant personality can best be conveyed in his own words. For this reason the great length of these volumes fully justifies itself. Each letter and each reference in it is fully documented by Dr. Butterfield, their editor. The result is an admirable commemoration alike of Rush, of his *alma mater*, Princeton University, and of the American Philosophical Society.

It is, however, impossible within the limits of this column to give more than a couple of extracts from the hundreds of letters in these volumes, many of which are quite thrilling. Two of medical interest must suffice.

A Slave Freed

"To the Pennsylvania Abolition Society.

"Philadelphia, November 14, 1788.

"There is now in this city a black man of the name of James Derham, a practitioner of physic, belonging to the Spanish settlement of New Orleans on the Mississippi. This man was born in a family in this city in which he was taught to read and write and instructed in the principles of Christianity. When a boy, he was transferred by his master to the late Dr. John Kearsly, Jr., of this city, who employed him occasionally to compound medicines and to perform some of the more humble acts of attention to his patients.

"Upon the death of Dr. Kearsly, he became (after passing through several hands) the property of Dr. George West, surgeon to the Sixteenth British regiment, under whom, during the late war in America, he performed many of the menial duties of our profession. At the close of the war he was sold by Dr. West to Dr. Robert Dove, of New Orleans, who employed him as an assistant in his business, in which capacity he gained so much of his confidence and friendship that he consented to liberate him, after two or three years, upon easy terms. From Dr. Derham's numerous opportunities of improving in medicine, he became so well acquainted with the healing art as to commence practitioner at New Orleans under the patronage of his late master. He is now about twenty-six years of age, has a wife but no children, and does business to the amount of three thousand dollars a year.

"I have conversed with him upon most of the acute and epidemic diseases of the country where he lives, and was pleased to find him perfectly acquainted with the modern simple mode of practice in those diseases. I expected to have suggested some new medicines to him, but he suggested many more to me. He is very modest and engaging in his manners. He speaks French fluently and has some knowledge of the Spanish language."

Strong Armchair

"To John Redman Coxe.

"September 5, 1810.

"Dear Sir,

"In attending the maniacal patients in the Pennsylvania Hospital, I have long seen with pain the evils of confining them, when ungovernable, by means of what is called the mad shirt or straight waistcoat. It generally reduces them to a recumbent posture, which never fails to increase their disease. In this state they often lie whole days and nights, and sometimes in a situation which delicacy forbids me to mention. The straight waistcoat moreover renders it impracticable to feel their pulses or to bleed them without taking off the greatest part of it. To obviate these evils and at the same time to retain all the benefits of coercion, I requested, by permission of the sitting managers of the Hospital, Mr. Benjamin Lindall, an ingenious cabinetmaker in this city, to make for the benefit of the maniacal patients a strong armchair, with several appropriate peculiarities as noticed in the drawing which I have herewith sent you for your *Museum*. From its design and effects I have called it a TRANQUILLIZER."

And lastly, as a timely warning to all medical men, a letter to his son:

"To James Rush.

"Philadelphia, November 18, 1803.

"My dear Son,

"Herewith you will receive your boots. They will serve I hope two purposes: 1st, to keep your feet and legs warm during the winter, and 2ly, to remind you that you have a father and mother in Philadelphia who have never forgotten you for a *whole week* since you came into the world. O fie—O fie, James!

"I never knew an instance of a man becoming eminent, respectable, or even wealthy in the profession of medicine who was deficient in punctuallty in letter writing.

"Adieu! From your affectionate though neglected parents,

"Benjn. and Julia Rush."

Let those who object to writing certificates take this to heart.

The reviewer feels that he must not end without assuring the reader, what he will have already gathered, that Dr. Butterfield has produced a work of first-class importance for the general history of the late eighteenth century. It is perhaps the most important contribution to American history that has been made for a good many years. It is impossible, however, to do justice to that aspect here.

CHARLES SINGER.

Correspondence

Modern Anaesthesia in Prostatic Surgery

SIR,—In the recent discussion on prostatic surgery in your columns, little has been said of the contribution to success made by modern anaesthesia. Indeed, it may well be that safe anaesthesia is every bit as important as the anatomical route of operation or the degree of operative precipitancy shown in these cases. In our department we have lately been using a combination of low spinal analgesia with regional analgesia of the abdominal wall for prostatectomy. This method was advocated by Gordon-Taylor.[1] Rowbotham,[2] who attributed the method to Jennings Marshall, emphasized its value in minimizing bleeding. It seems, however, that such a technique is not widely used at present.

Our procedure has been as follows: After a pre-operative injection of morphine ¼ gr., spinal anaesthesia is administered in the sitting position. The fourth/fifth lumbar space is used; 0.5 to 0.75 ml. of "nupercaine" (cinchocaine 1:200) is injected without barbotage. The patient is kept sitting for five minutes and is then placed in the supine position. The solution used for the infiltration of the lower abdomen is conveniently made by mixing 20 ml. of a 2% solution of "xylocaine" (lignocaine) with 140 ml. of normal saline, and then adding the contents of a ½-ml. ampoule of adrenaline 1:1,000. The injection is usually made by the anaesthetist, but, if not practicable on account of obesity, the solution is injected layer by layer by the surgeon.

In our short series of cases the operations have been either retropubic (6) or transvesical (14). One transvesical operation included a segmental bladder resection. Ten operations have been emergencies for acute retention of urine (transvesical, 6; retropubic, 4). The patients have ranged in age from 57 to 84 years, six being octogenarians. All have tolerated the procedure well, though one patient complained of some discomfort during enucleation of the gland by the retropubic method, where it was recognized that there had been an error in technique. In all the circulation has remained good and bleeding has been slight. All the patients have been able to drink copiously from the moment of their return to the ward.

Many authorities condemn spinal anaesthesia for prostatectomy on two grounds: (1) that the fall in blood pressure carries a risk of reactionary haemorrhage; and (2) that the bladder, for some hours after operation, loses its power to expel its contents through the drainage tube, so that the risk of clot retention is increased (Magill[2]). Rowbotham[3] stressed that with low spinal anaesthesia vasoconstriction in the prostatic bed and contraction of the prostatic cavity resulted from unopposed sympathetic action following paralysis of the sacral autonomic nerves. Forrester[4] maintained that extension of the "low spinal" to include the third lumbar segment, planned to leave unaffected the sympathetic fibres arising in the first and second lumbar segments, still allowed incisions to be made in the lower abdomen. As the skin of the lower abdomen is innervated from the tenth thoracic to the first lumbar segments, it seems that spinal anaesthesia allowing such incisions to be made would of necessity inactivate some of the sympathetic outflow. The advantages of a sustained systemic blood pressure and of unopposed vasoconstrictor action in the prostatic bed would then be lost.

We favour the use of spinal analgesia confined to the sacral segments in order to diminish bleeding without depressing systemic blood pressure. The regional analgesia of the lower abdominal wall produces less disturbance than even the best general anaesthetic. The combination of both is well tolerated by the elderly, bad-risk prostatic patient and seems worth an extended trial.—We are, etc.,

H. W. LOFTUS DALE.
R. B. CLAYTON.
W. R. PROBERT.

Aylesbury.

REFERENCES

[1] *Proc. roy. Soc. Med.*, 1944, 37, 533.
[2] *Retropubic Urinary Surgery*, 1947. E. and S. Livingstone, Edinburgh.
[3] *Anaesthesia*, 1946, 1, 70.
[4] *Brit. J. Urol.*, 1947, 19, 176.

Sterility after Lumbar Ganglionectomy

SIR,—In his article (January 31, p. 247) Mr. S. S. Rose rightly draws attention to the fact that male patients are certainly by no means invariably sterile after a resection of the lumbar paravertebral sympathetic chain which includes the first lumbar ganglion. Indeed, he describes one of his cases of extensive sympathectomy who was later able to produce a seminal emission, and he mentions three cases in the literature. We should like to report a similar patient who not only has been able to produce semen but has achieved paternity.

This patient has been followed up for three and a half years after the operation of bilateral paravertebral sympathectomy and splanchnicectomy for hypertension. The resection included T_{9}–L_{2} ganglion on the right side, but at the second operation two months later technical difficulties prevented the resection from being carried with certainty above the T_{10} level, but the lower end included the L_{2} ganglion. Three months after the operation on the right side and three weeks after that on the left, the patient was tested for residual sweating by the electrical skin resistance method after first heating until he was sweating freely. The patterns showed complete denervation in the L_{4}–S_{2} dermatomes on both sides and in T_{4} to approximately T_{10} dermatomes on the right thorax, but only about T_{10} and T_{11} dermatome on the left thorax (Boyd, J. D., and Monro, P. A. G.[1]).

Subsequent testing 19 months after the first operation showed an essentially similar pattern, except that the edges of the anhidrotic areas were less irregular and the area of anhidrosis on the left side after injection of carbachol consisted of a single belt on the flank extending to within about two inches of the midline front and back. At this time the patient stated that he thought he was producing semen on intercourse, but, though he experienced orgasm, this was not accompanied by *rhythmic* ejaculation. His child was born 16 months later. ABO grouping is not incompatible.

More recent testing 42 months after the first operation shows that the sweating pattern on the right side is unaltered, but on the left thermoregulatory sweating is now present in the axillary line in about a 2 in. (5 cm.) wide strip across the belt of previous anhidrosis in the T_{10} T_{11} dermatomes—thus indicating a partial recovery of sympathetic function at this level. The anhidrosis in the L_{4}–S_{2} dermatomes remains unchanged on each side.

In an article (Boyd and Monro[1]) it has been shown that the "escape area" in the L_1 and L_2 dermatomes—with probable overlap into the T_{12} and L_3 dermatomes—is supplied by ganglion cells situated in the lumbar intermediate sympathetic ganglia which, because of their inaccessible position in close proximity to the nerve roots, have survived the paravertebral sympathetic resection. A sweating test will therefore not indicate whether or not any part, or whole, of the paravertebral sympathetic chain from the level of T_{12} to L_3 has been left behind. In this particular case it seems to us more probable, in view of the partial return of sympathetic function to the left T_{10} T_{11} dermatomes after three years, that the recovery of sympathetic control of the pelvic viscera has been by regeneration of preganglionic pathways from T_{11} nerve root (at the lowest) on the left side. A possible alternative pathway could be from intermediate ganglia related to either L_1 or L_2 nerve roots. Serial section of post-mortem material has shown that such a pathway from intermediate ganglia may be traced along the course of the lumbar arteries towards the aorta, and that these fibres had escaped section. Though it is possible that this pathway might contain preganglionic fibres to the mesenteric ganglia it appeared more probable that the fibres in this bundle, which was very small, were mostly distributed to the blood vessels (Monro[2]). Seminal anorrhoea is the usual finding after extensive sympathectomy, but the presence of lumbar intermediate sympathetic ganglia is invariable. It therefore does not appear that after paravertebral sympathectomy these intermediate ganglia easily establish functional communication with the pelvic viscera.

The upper level of sympathetic denervation to be found after bilateral resection of the paravertebral ganglia L_1, L_2, and L_3, as shown in Mr. Rose's paper, appears to lie at the lower edge of the L_1 dermatome. We cannot agree that

this is the usual level to be found on thermoregulatory sweating. Our findings confirm the earlier observation of Ray and Console.[3] In over 90% of our cases which have undergone resection of L_3, L_2, and L_1 paravertebral ganglion or above, the lower level of sweating has included the inner side of the knee, and indeed in about 80% it has also included the inner side of the calf to just above the ankle—L_3 dermatome. The discrepancy of sweating patterns in Mr. Rose's cases and ours is probably due to technique. In all our observations the patient is first heated until the rise in body temperature causes free sweating in all areas that still retain an intact sudomotor pathway. According to the method described by Ratcliffe and Jepson,[4] no such precaution is taken, and accordingly only a relative change in the degree of sweating is indicated.

It therefore appears that when lumbar sympathectomy is to be performed for peripheral vascular disease of the lower limbs, provided always that the resection includes the lower level of the preganglionic outflow (usually L_2 but rarely L_3), little advantage is to be gained in resecting the paravertebral chain up to the level of L_1. The skin vessels will not be denervated over any greater area; those in the upper thigh will not be completely denervated, since they are still supplied by intermediate sympathetic ganglia in which, at this level, we have counted approximately 7,000 cells associated with L_1 nerve root. This residual innervation may be less rich than normal, but there is no evidence to show that vasomotor tone is significantly decreased. Similarly, vasomotor tone is still present on the inner side of the calf after any degree of paravertebral lumbar sympathectomy. Ulceration here will tend to persist, though it may heal on the outer side of the foot when this is truly sympathectomized. After resection of L_1, L_2, and L_3 ganglia on the right and L_2 L_3 only on the left, the sweating patterns are symmetrical. It must remain a matter of opinion whether removing the L_1 paravertebral ganglion containing about half of the sympathetic ganglion cells supplying the upper thigh will improve the blood supply to the limb sufficiently to justify the risk of seminal anorrhoea.—We are, etc.,

D. W. C. NORTHFIELD.
P. A. G. MONRO.

London, E.1.

REFERENCES

1 *Lancet*, 1949, 2, 892.
2 *J. Anat. (Lond.)*, 1951, 85, 417.
3 *J. Neurosurg.*, 1948, 5, 25.
4 Ibid., 1950, 7, 97.

Ganglionic Blockade with Methonium Compounds

SIR,—The application of methonium compounds as ganglionic blocking agents in producing a controlled hypotensive state during surgical procedures has recently evoked great interest among surgeons and anaesthesiologists. A blockade of the autonomic nervous system without producing a fall in blood pressure can be of value during haemorrhage and in the conduction of anaesthesia.

It has been shown experimentally that rats treated with minimal doses of piperoxan hydrochloride ("dibenamine") and subjected subsequently to haemorrhage withstand the blood loss better than those who have not received any medication; 92% of the treated animals survived as contrasted to 28% survival for control rats.[1] The explanation is that the vasoconstrictive phase of the early haemorrhagic shock has been prevented. My clinical experience with patients who have received sub-hypotensive doses of hexamethonium bromide (C_6) during radical surgical procedures, and who were subjected to appreciable blood loss corrected by transfusions, leaves me with the impression that the blockade of the autonomic nervous system was of benefit. These patients did not display the picture of shock that has often been seen with other patients under the same circumstances but who did not receive C_6. The sub-hypotensive doses of hexamethonium bromide—i.e., those producing ganglionic blockade to a degree which will not lead to a drop in blood pressure—can be determined prior to operation by the amount needed to abolish the psychogalvanic reflex in one of the arms. If the latter has not been done, C_6 can be given at the start of anaesthesia in very small doses, 1.0–2.0 mg. at a time, until the pupils become dilated, showing that ganglionic blockade has occurred.

Abolishing or diminishing the autonomic nervous system reflexes will also be of benefit during the various phases of anaesthesia and surgery such as intubation, pressure on coeliac plexus or carotid sinus, traction on peritoneum, etc. It would seem that the ganglionic blockade represents a new field in modern anaesthesiology which is well worth further exploration.—I am, etc.,

New York. PAUL BOYAN.

REFERENCE

1 Shorr, E., *et al.*, *Fed. Proc.*, 1952, 11, 177.

Thrombo-angiitis Obliterans

SIR,—In his excellent article (February 28, p. 478) Dr. R. L. Richards has referred to an article on the subject which I published in 1916.[1] I hope I shall not be considered ungracious if I say that I should have preferred a mention of an article which I published much earlier,[2] apparently before any of Buerger's publications on the subject (compare my *Endocrine Tumours and Other Essays*, 1936, H. K. Lewis, London). I do not of course dispute the justice of the name "Buerger's disease," for his article, illustrated by so many exact pathological descriptions, sprang like Athene fully armed from out of the head of her father Zeus. That Buerger, as I did myself, thought at first that the disease was almost exclusively confined to males of Jewish families may be in part explained by the fact that he worked at a great Jewish hospital in New York, as I worked at a hospital situated close to the centre of Jewish immigrant life in London.—I am, etc.,

London, N.W.1. F. PARKES WEBER.

REFERENCES

1 *Quart. J. Med.*, 1916, 9, 289.
2 *Lancet*, 1908, 1, 152.

Pethidine Poisoning

SIR,—Dr. C. Romer's description of a case of acute pethidine poisoning[1] prompts us to describe another one exhibiting certain differences.

This patient was a man aged 53 and known to be a chronic osteoarthritic, who had been found comatose in his bed one morning. On admission here he was semi-comatose, perspiring freely, and having irregular twitchings of both arms and legs. There was increased tone in the lower limbs, absent knee-jerk reflexes, and a left Babinski plantar reflex. The upper limb jerks were present and equal. The pupils were small, equal, and regular, and did not react to light. The respirations were 36 per minute, the pulse rate 150 per minute, the blood pressure 150/100, and temperature 100.5° F. (38.05° C.). He was given a simple sedative (pot. brom. et chloral.). Some eight hours later, although still confused, he stated he had taken contrary to the strict instructions of his medical advisers 40 tablets of pethidine, which had been prescribed to relieve his arthritic pains. He was still perspiring freely and his respirations were 32 per minute, but the muscle twitching was less and the blood pressure had risen to 210/120. The following day he was completely recovered (36 hours after taking the drug). Urinary pethidine estimations were made on two samples (the only ones available) passed at the 36th hour and the 40th. The former (volume 162 ml.) contained 0.925 mg.% and the latter (162 ml.) 0.113 mg.% of the drug. The serum (40th hour) contained only a trace. The technique employed was a modification of Lehmann and Aitken's method.[2]

This case differs, therefore, from Romer's by the predominance of the stimulatory action of pethidine—tremors, muscular twitchings, profuse sweating, and rapid respirations. Clearly intravenous injection of nikethamide would have been contraindicated. Romer's suggestion of empirical injection of this drug into patients comatose from suspected, albeit unknown, poisoning should be restricted to those with respiratory depression. Barbiturates would be the treatment of choice in a case with marked stimulatory overaction (Way[3]). Of interest also is the marked fall of the blood pressure. Pethidine is an acknowledged cardiac depressant (Duguid and Heathcote[4]), and this action is

directly on the myocardium. There is a further depressant action to the cardiac vagus (Way and Ligon[5]). The rapid excretion of the pethidine, as indicated by the very low urinary and serum levels at the 36th hour, conforms to the expected pattern (Donatelli and Di Lollo[6]). As in Romer's case, the pupils were small, and there was no vomiting. On further investigation, we found that the patient's pethidine tablets each contained 50 mg. of this drug, and that he had therefore taken 2,000 mg. of pethidine, the largest recorded single dose ever taken. Cohen's patient[7] took 1,250 mg., and Romer's 1,500 mg. All three patients recovered.

We are much indebted to Dr. R. G. M. Longridge, in whose care the patient was, to Dr. L. H. D. Thornton for his advice, and to Mr. H. B. Salt for his help and details of the pethidine estimation.—We are, etc.,

J. R. H. PINKERTON.
D. W. M. ROLFE.

Salisbury.

REFERENCES

1 *British Medical Journal*, 1952, 2, 1135.
2 *J. Lab. clin. Med.*, 1943, 28, 787.
3 *J. Pharmacol.*, 1946, 87, 265.
4 *Quart. J. Pharm.*, 1940, 13, 318
5 *J. Amer. pharm. Ass.* (Scient. Ed.), 1946, 35, 113.
6 *Sperimentale*, 1947, 98, 590.
7 *Ann. Allergy*, 1950, 8, 547.

Primary Red-cell Aplasia

SIR,—We have read the article on a case of primary red-cell aplasia by Dr. Michael Donnelly (February 21, p. 438) with great interest, as we have an almost identical case under our care at present.

A male infant, now 10 months old, was first seen at the age of 13 weeks, when a blood count showed haemoglobin 17% (2.52 g.%); red cells 610,000; leucocytes 4,000, with 25% polymorphs. In the stained film the red cells showed anisocytosis, poikilocytosis, and macrocytosis, and occasional normoblasts were found. Pregnancy and delivery had been normal and there are two other healthy children. Father and mother are healthy but elderly, and there is no family history of anaemia. Treatment with oral iron, vitamin B_{12}, and ascorbic acid produced no improvement, and several blood transfusions were given, the haemoglobin falling regularly after each transfusion. Apart from the anaemia the infant remained cheerful and well and continued to gain weight.

On admission to hospital for further investigation on October 24, 1952, a blood count showed haemoglobin 40% (6.3 g.%); red cells 2,100,000; leucocytes 18,900, with 74% polymorphs. Reticulocytes 1%. Blood group O rhesus negative, with no incompatibility between infant's cells and mother's serum (group O rhesus positive) by indirect Coombs test. Bone marrow (iliac crest) showed an extremely cellular marrow with marked myeloid hyperplasia. Red-cell precursors were virtually absent, a few polychromatic erythroblasts being found only after prolonged search of several preparations; the Wassermann was negative and chest *x*-ray examination and urine were normal. Since then the infant has been readmitted on several occasions for further blood transfusions. Two further examinations of bone marrow have shown a complete absence of red-cell precursors in a cellular myeloid marrow. Reticulocytes can no longer be demonstrated in the peripheral blood. The infant has remained well apart from a recent upper respiratory tract infection with early bronchopneumonia. This responded normally to penicillin and chloramphenicol.

In this case one must conclude that some functioning erythropoietic tissue was present up to the age of 6 months, as both normoblasts and reticulocytes could be found in the peripheral blood. Since then the absence of reticulocytes in the blood and the complete absence of red-cell precursors in the bone marrow would suggest that all erythropoiesis has now ceased in this patient.—We are, etc.,

A. G. V. ALDRIDGE.
P. KIDD.

Worcester.

Vitamins and the Boat Race

SIR,—It transpires from the columns of a well-respected national daily newspaper that the training regime of the Cambridge boat crew includes taking vitamin pills. Vitamins are an essential treatment of vitamin-deficiency diseases and are especially valuable when there is fear of vitamin deficiency, such as in early childhood or during pregnancy. I think it unlikely that the Cambridge crew will fit into any of these categories.

The amount of energy, labour, material, and advertising designed to persuade the public to consume, and the medical profession to prescribe, a daily dose of vitamins of various kinds is phenomenal. The argument runs somewhat like this: "Pain in the little finger is an early sign of vitamin-blank deficiency. Therefore, anybody who ever gets a pain in the little finger should take vitamin blank daily. Even if you haven't got a pain in your little finger vitamin blank taken daily will prevent you getting one." It is also unfortunate that the word vitamin should suggest that it is somehow connected with giving vitality.

An official statement from an authoritative source on the limitations of vitamins would not come amiss. In its absence I will stick my neck out with the following pronouncement. A daily supplement of vitamins is valueless to the normal adult. In particular there is no evidence to show that it will prevent coughs and colds (American papers, please copy). The high-dosage vitamin treatment of certain diseases where the vitamin is used like a drug is of course an entirely different subject.—I am, etc.,

A. LEWIS.

London.

Effect of Isoniazid on Carbohydrate Metabolism

SIR,—In view of the article by Dr. G. R. W. N. Luntz and Mr. S. G. Smith (February 7, p. 296) on the association between carbohydrate metabolism and isoniazid therapy, the following case report may be of some interest. The patient apparently developed diabetes mellitus during a course of isoniazid therapy for pulmonary tuberculosis. Cause and effect have not been proved, however, and the case is presented without comment.

A male, aged 36, with no family history of diabetes mellitus, first reported at a general medical out-patient clinic with dyspeptic symptoms on June 16, 1952, and was found to be suffering from pulmonary tuberculosis. *X*-ray examination showed infiltration and cavitation in the right upper lobe, calcium deposits at the right hilar region, and soft mottling, especially peripherally, throughout the left lung. Acid-fast bacilli were found in direct smears of his sputum. Urine contained no albumin, and Benedict's test did not reveal any reducing substance. He was transferred to the care of the Hammersmith Chest Clinic and admitted to the ward on July 11, where he was accepted for the current M.R.C. chemotherapy trial.

On July 19 chemotherapy was commenced with streptomycin 1 g. daily by intramuscular injection and isoniazid (given as "nydrazid," Squibb) 100 mg. twice daily. This was continued for three months to a total dosage of 94 g. streptomycin and 18.8 g. isoniazid. Both clinical and radiological improvement occurred on this regime, and it was felt that chemotherapy could now be suspended and that the patient should remain under close observation on bed rest alone pending admission to sanatorium for probable surgery. The urine contained no albumin, and weekly testing with Benedict's solution revealed no reducing substance from July 11 to September 14, but on September 21, during the course of treatment, when 65 g. streptomycin and 13 g. isoniazid had been given, it was first noticed on ward test that the patient's urine turned Benedict's solution yellow. Ward tests on succeeding days produced colours varying between green and orange. On October 2 a glucose tolerance test was performed and resulted as follows:

	Blood Glucose (mg./100 ml.)
Before glucose	264
½ hr. after	406
2 hrs. ,,	330
2½ ,, ,,	292

Before glucose ingestion, 45 ml. of urine contained 3.7 g. glucose. Two hours after ingestion, 47 ml. of urine contained 3.1 g. glucose.

Isoniazid therapy was maintained until the end of the three months' course of treatment, but the patient was placed on a 200-g. carbohydrate diet and P.Z. insulin 18 units daily. At the

end of his course of chemotherapy the P.Z. insulin (as well as the isoniazid therapy) was discontinued. After two weeks without insulin or isoniazid the glucose tolerance test was repeated and showed:

	Blood Glucose (mg./100 ml.)
Before glucose	200
1 hr. after	304
2 hrs. ,,	366
2½ ,, ,,	328
3 ,, ,,	305

Urine specimens examined during the glucose tolerance test showed:

	Amount	Containing Total Glucose
Fasting	132 ml.	338 mg.
After 1 hr.	20 ,,	190 ,,
,, 2 hrs.	45 ,,	2·1 g.
,, 2½ ,,	56 ,,	3·1 ,,
,, 3 ,,	46 ,,	2·9 ,,

Following this investigation, the patient was restabilized on insulin P.Z. 32 plus soluble 12 each morning and treated as an ordinary diabetic. He was allowed home for further bed rest only, but readmitted on January 19, 1953, for further reassessment over a period of a week as laid down for the M.R.C. isoniazid trial. This was six months after commencing his three months' course of chemotherapy.

On admission his clinical condition was very satisfactory and the sputum was negative on direct smear examination. The radiograph showed no further change in the tuberculous lesion. The insulin requirements had fallen and the patient was restabilized on P.Z. 24 units and soluble 6 units daily.—We are, etc.,

CYRIL EVANS.
London, W.12. PETER STRADLING.

The Young Delinquent

SIR,—In the review of my book *Juvenile Delinquency*, Sir Cyril Burt (February 7, p. 317) very properly points out my slip with regard to Dr. H. H. Goddard. The corrected sentence should of course read: "Some of the more outstanding contributions to this development have been made by Sir Cyril Burt in this country; by H. H. Goddard, W. Healy, and . . . in the United States of America. . . ."

I have not, however, fallen into the error, as he suggests, of saying that intelligence quotients and similar devices were not used in clinics for diagnostic purposes before World War II. What I have said is that since World War II intelligence quotients and personality profiles have for the first time been assessed in many hospitals and clinics as an essential part of any psychiatric diagnostic procedure. During the past few years there has been a great development in the use of these and similar techniques in clinical practice, as most medical practitioners know full well.—I am, etc.,

London, W.1. J. D. W. PEARCE.

Sympathectomy for Recurrent Albuminuria of Pregnancy

SIR,—The problem of recurrent albuminuria of pregnancy with repeated stillbirth in the seventh or eighth month of successive pregnancies has long exercised the minds of obstetricians. Mr. G. W. Theobald is greatly to be congratulated upon his imagination and enterprise in devising a perivascular sympathectomy operation (February 21, p. 422) to increase the uterine blood supply and thus provide an answer. His pilot survey of three cases is at least suggestive that the operation deserves a more extensive trial. However, it is my experience that a young primigravida with toxaemia of pregnancy, as opposed to hypertensive disease, will almost invariably remain free from recurrence in her next pregnancy however early the albuminuria developed in her first. As hypertensive disease and toxaemia are often difficult to distinguish, I believe that Mr. Theobald should have laid even more emphasis upon the need for two albuminuric stillbirths before his operation was indicated.

I have recently had under my care two young primigravidas with alarming toxaemia at the twenty-fourth week of pregnancy. In one case hysterotomy was undertaken, while the other delivered herself after the insertion of laminaria tents. Both were encouraged to become pregnant again without delay despite a residual hypertension of 140/90 in one case. Both had uneventful pregnancies without albuminuria one or two years later. Unless the strictest criteria are laid down for the indications for this operative procedure it will be impossible to assess its true value.—I am, etc.,

Birmingham. W. G. MILLS.

Prophylaxis of Tetanus

SIR,—As a comment upon Dr. Leslie Cole's Refresher Course article on tetanus (January 17, p. 150), may I suggest that the real solution of the whole problem of prophylaxis lies in a combined diphtheria–tetanus toxoid given in the first year of life with a "boosting" dose later? I believe the public would readily accept this, and the cost would not, I think, be prohibitive even if it became universally accepted, for it would be spread out over the years. It should, if adopted, gradually wipe out the death rate from tetanus, which, after all, is about twice that from diphtheria at the present time, and there would at least be a great saving in respect of serum.

It is no reflection upon medical officers of health to suggest that pressure to secure this valuable extension of preventive medicine must come from the general practitioner, who is always in a potentially vulnerable position in regard to tetanus. If he sees the wound soon after it is inflicted and does not give serum, and the patient later develops tetanus, he is very likely to be blamed, whereas if anaphylaxis comes like a bolt out of the blue, as it can after a dose of serum, he is not likely to be popular.—I am, etc.,

London, N.W.7. A. H. MORLEY.

A Journal and its Readers

SIR,—Surely your leading article on this subject (February 28, p. 496) must give rise to deep thought amongst many of your readers. To me, at any rate, it seems to be more an apology for the general layout and contents of the *Journal* than anything else. Certainly the original work is refreshing for those who have the time to read it; but how many of us have? The correspondence columns sometimes contain interesting letters when these are not crowded out by the uninteresting, and the *Supplement* when it was separated from the *Journal* was a ready guide to current medical politics.

Considering what an overwhelming number of your members are general practitioners, it is amazing how little of real interest to them appears therein. You may say there are the "Refresher Courses," but if you come to read them how many of them avoid the technical and keep to the simple and produce something easy to read and remember?

Let me compare the article on "Tachycardia" in the *Journal* (February 28, p. 500) with that on "Recent Advances in Geriatrics" (*Medical World*, December 5, 1952), which was an object lesson in clarity and usefulness. I could give many more.—I am, etc.,

Worthing. HAROLD LEESON.

SIR,—Dr. J. M. B. Morwood (March 14, p. 620) laments that the *Journal*, in his opinion, fails to produce very much for anybody.

Until qualified, the student's tastes in medicine must remain catholic. This being so, he is amongst the *Journal's* most important readers. Popular demand dressed the

"Refresher Course" series of articles in book form. The implied insult in this title is very hard to see. Whatever one's chosen path in the healing art and success on it, the most and best one can claim is to remain a student of it.—I am, etc.,

London, N.1. DUNCAN D. MACDONALD.

Cross-resistance between "Daraprim" and Proguanil

SIR,—A letter from Drs. G. I. Robertson, D. G. Davey, and Sir Hamilton Fairley (December 6, 1952, p. 1255) reported that a proguanil-resistant strain of *Plasmodium falciparum* from Malaya had proved to be resistant also to pyrimethamine ("daraprim"). Proguanil-resistance in Malayan strains of *P. falciparum* has been recognized since 1949[1]; and if a true cross-resistance exists, this might—as implied by Dr. J. S. K. Boyd (February 7, p. 337)—go far to explain the pyrimethamine failures described in our paper (January 31, p. 253).

Proguanil has been so widely used throughout Malaya for the past six years that there can be few strains of parasite which have not yet come into contact with it; thus there is little chance of deciding now how the "parent" strains (without previous contact with proguanil) might have responded to pyrimethamine. We have not, however, been able to confirm that there is any consistent cross-resistance between these two drugs in naturally acquired falciparum malaria since pyrimethamine was first used in Malaya in 1951. Pyrimethamine failures have been successfully treated with normal doses of proguanil, and proguanil-resistant infections have responded readily to pyrimethamine. In some of these cases an interval of several days was allowed to elapse between treatments, so the possibility of a combined action of the two drugs should have been small.

We consider that these apparently conflicting results can best be explained by assuming that some present-day strains of *P. falciparum* in Malaya possess a "natural" resistance to pyrimethamine, whether or not any particular strain is also demonstrably resistant to proguanil. With this species of parasite, a true cross-resistance has still to be proved.—We are, etc.,

T. WILSON.
J. F. B. EDESON.

Kuala Lumpur, Malaya.

REFERENCE

1 *British Medical Journal*, 1950, 1, 147.

"Butazolidin"

SIR,—The first clinical report on butazolidin was made, not in the U.S.A., as you state in your leading article (December 27, 1952, p. 1401), but by Dr. John Currie at the European Rheumatology Congress, Barcelona, in September, 1951.[1]

You ask whether butazolidin is merely a potent analgesic or whether it has specific anti-rheumatic action. The following considerations after 200 cases have left me in no doubt that it has a specific effect on rheumatic inflammation. Pains from sources other than joints and muscles, such as sciatic pain from carcinoma of pancreas, cellulitis, and psychogenic rheumatism, have not been relieved. In five rheumatic patients acute gastric pain has been brought on by butazolidin, while joint pains have been relieved. In 20 cases acute swelling of a single joint has subsided dramatically at the same time that the pain has been relieved. The joints were not rested; several acutely swollen knees and ankles subsided while the patient continued to walk about.

I do not believe that we have any means—other than low dosage and careful clinical observation—of preventing or forestalling toxic side-effects. I have not found any abnormalities in the blood in 35 patients with nausea, rashes, or oedema. Therefore the patient's own symptoms are the safest guide to toxicity. Granulocyte counts have remained consistently normal in a total of more than 1,000 cases reported by various authors; Steinbrocker and others[2] detected five cases of neutropenia, but in three the count returned to normal with continued butazolidin treatment. Lowering of platelet counts—reported by Currie[3] and Stephens and others[4]—was not associated with purpura or any other untoward symptoms; in the single case of purpura reported by Rhys Davies and others[5] the platelet count was normal.

Routine and repeated counts of platelets and granulocytes are laborious, and they may lead us astray because we do not know the hour-to-hour and day-to-day fluctuations of platelets and granulocytes in the normal subject. Laboratory observation of the blood should not be mandatory, and failure to observe this precaution should not be regarded as neglect.—I am, etc.,

Melbourne, Australia. MICHAEL KELLY.

REFERENCES

1 *Communications to Second European Rheumatology Congress*, 1951, p. 417.
2 *J. Amer. med. Ass.*, 1952, **150**, 1087.
3 *Lancet*, 1952, **2**, 15.
4 *J. Amer. med. Ass.*, 1952, **150**, 1084.
5 *British Medical Journal*, 1952, **2**, 1392.

"Unfit for Military Service"

SIR,—May I endorse the letter of Dr. A. Barham Carter (February 7, p. 334) and take the point he raised one step further? As a regimental medical officer I am frequently called upon to interpret certificates given to Service personnel who are sick on leave which are either unreadable or couched in technicalities which give no indication as to the seriousness (or otherwise) of the soldier's illness.

It also does not appear to be widely known that Service personnel sick on leave must produce, on return to their unit, a certificate stating that they were *unfit to travel* at the termination of their leave. Failure to do so, or to provide other suitable evidence, may result in disciplinary action being taken against the man concerned. Minor ailments which do not prevent the man from travelling are not accepted as an excuse for absence.

May I therefore put in a plea to practitioners treating these patients to write their certificates in plain language, and state that the patient was fit, or unfit, to travel on the dates concerned, so that his commanding officer can assess the case in its proper light?—I am, etc.,

Walton-on-Thames. C. D. ELTON.

Nicotinic-acid Deficiency in Psychiatric Practice

SIR,—Increasing attention is now being paid to the large numbers of psychiatric patients who exhibit signs and symptoms suggestive of deficiency of the vitamin-B group, and articles by Jolliffe *et al.*,[1] Wadsworth *et al.*,[2] Sydenstricker and Cleckley,[3] Washburne,[4] and Gregory,[5] among others, are worthy of study. The following account of a recent psychiatric case admitted to hospital may be of interest as being illustrative of such deficiency states.

A man aged 43 was admitted to hospital in a stuporose condition on October 9, 1952. He was restless, agitated, and confused, and resisted all attempts to feed him, examine him, or converse with him. He was also depressed, emotional, and actively suicidal. Physically he was in an extremely weak and emaciated condition, quite unable to stand, and with a coarse tremor of his tongue and limbs. His skin was dry, scaly and atonic, and there were large patches of dermatitis on his abdomen and back, smaller ones on the backs of his knees and elbows, and also on his wrists, hands, and feet. His lips were dry, sore, and cracked, his tongue was dry, red, raw, and fissured, and his teeth and gums were unhealthy and neglected. His stools were loose, he was doubly incontinent, and there was a huge bedsore as large as a tea plate over his sacrum.

His wife gave a history of gastric carcinoma first suspected in 1943 and successfully treated by partial gastrectomy. Early in 1952 he complained of dyspepsia, began to lose weight, and developed a terrible fear of recurrence of cancer. Despite negative findings with *x*-ray examination and reassurance he became increasingly depressed and introspective, refused all food, and finally was admitted to hospital because he was suicidal. He did not use his voice for some months prior to admission to hospital, but his speech was confined to incoherent whisperings about "cancer." He was diagnosed as suffering from a confusional state with marked depressive and phobic features, and on purely clinical grounds he was thought to have a nicotinic-acid deficiency of such a degree as to present almost a classical picture of pellagra. He was immediately given nicotinic acid 1,500 mg. intravenously in normal saline, and the effect was dramatic. The solution was injected slowly into a vein at the bend of the elbow,

and after an interval of two and a half minutes there was an intense reaction with marked flushing, first of the face and then of the trunk and limbs. The patient appeared to awaken from his lethargic state, conversed normally for about 15 minutes, and then slipped back into a state of torpor again. This treatment was continued daily, and after 24 hours he was co-operative and willing to take food and drugs orally. As his condition improved his diet was supplemented, and by the tenth day of treatment he had full volition and was co-operating well and conversing normally. Nicotinic-acid therapy was continued for 28 days, supplemented by oral vitamin "B-complex," and afterwards combined oral therapy was continued.

The results have been most gratifying. The patient is now up all day, is usefully employed in the hospital, and is bright and optimistic about the future. He has a good appetite, and his weight has increased by 2 stone (12.6 kg.) since admission. Within a month all his skin and mouth lesions had cleared up completely, and the huge ulcer crater over his sacrum is almost completely healed. He is now fit enough to return to his former employment.

Such a case is probably met with very infrequently in clinical practice, but minor degrees of nicotinic-acid deficiency are comparatively common in pre-senile and senile depressive and confusional states, and the signs and symptoms should be looked for and treated early, as the response is usually very gratifying.

I am indebted to Dr. L. Barber for permission to publish this case, and to Dr. D. C. Dewar for his help and advice.—I am, etc.,

Walton-on-Thames. G. H. COLLINS.

REFERENCES

1 *J. Amer. med. Ass.*, 1940, **114**, 307.
2 *Amer. J. Psychiat.*, 1943, **99**, 807.
3 Ibid., 1941, **98**, 83.
4 *Ann. intern. Med.*, 1950, **32**, 261.
5 *Amer. J. Psychiat.*, 1952, **108**, 888.

Attitude Surveys with Patients in Hospitals

SIR,—Since a contented patient is likely to regain physical health more quickly than one who is unhappy or frightened, it is important for responsible staff in hospitals—medical, nursing, and administrative alike—to know in detail the views of their patients. But hospitals are complex organizations, and it is difficult for the staff to obtain an accurate picture of the patients' attitudes towards all the various aspects of their stay in hospitals. The vocal patient is not necessarily the typical one. Whether the patients' views are favourable or unfavourable, whether they are based on fact or on misapprehension, they are equally important in their effect.

One method of gaining this information is by conducting attitude surveys by the "confidential individual interview method" with a representative sample of patients shortly before they are discharged. Such surveys are best conducted by an impartial outsider who can inspire confidence in the promise of anonymity, who has time to devote to the inquiry, and who has the special training and skill to get a flow of information without prompting or question. The procedure of conducting attitude surveys in hospitals would at first have to be experimental, but might follow some such lines as those indicated below.

The co-operation of the staff, medical, nursing, and administrative, would first be obtained so that they realized that the purpose of the survey was to give constructive help. Then a representative sample of patients would be interviewed, each as near to the time of discharge as possible. Before each patient was interviewed he would receive a letter from a senior member of the hospital staff urging him to co-operate. He would be asked to comment on all aspects of his stay in hospital, and told that what he said would be reported, but with no name mentioned. An account of the survey would give the hospital information on the views of its patients, analysed by ward, age, length of stay, etc. When a number of surveys had been made in different hospitals a general report could be prepared which, while preserving the anonymity of the hospitals concerned, would indicate matters found common to many hospitals that could be altered for the benefit of the patients.

Considerable interest has been expressed in this scheme by the doctors, nurses, and administrators with whom it has been discussed, and a pilot survey has been undertaken. It is hoped that more hospitals will be ready to collaborate in it.—I am, etc.,

London, W.1. WINIFRED RAPHAEL,
Assistant Director,
National Institute of Industrial Psychology.

Bilateral Cough Fractures

SIR,—Articles by Dr. J. B. Mitchell[1] and Dr. N. Wynn-Williams[2] and subsequent correspondence drew attention once again to cough fractures as a cause of pain in the chest. There has been no mention of the fact that these fractures can, on occasion, be bilateral: a search of the literature shows that no cases of this type have been described in this country and only four articles in the American literature record such fractures. Howson[3] quotes one case with three fractures on the right side and one on the left. Richardson,[4] reviewing 1,903 patients, found 30 cases with cough fractures, in which four were bilateral. Swineford and McKinnon[5] quote a patient who fractured eight ribs in six months, three on the left side and five on the right. Bodenheimer,[6] reviewing the literature up to that date, gives a figure of 4% as the incidence of bilateral fractures. Details of two further cases are given below.

The first patient, a woman schoolteacher aged 25, became ill early in December and was sent to the school sanatorium: she was told she had "congestion of the lungs." About December 8 she coughed while bending over to pick up her bedroom slippers from under the bed, and felt an acute pain in her left side. This was treated with poultices. On December 15 she was allowed up to help pack her luggage for the Christmas holidays, and while bending over her case she coughed and had quite severe pain in her right side. She came home on holiday and was sent to hospital for an *x*-ray examination of her chest on January 2. This showed recent fractures of the 8th and 10th right ribs and the 10th left rib. The patient was quite unaware of these fractures and had felt no pain since Christmas.

The second patient was a woman aged 39 who had "bronchitis" for several weeks and developed pain in the left side of her chest. *X*-ray examination in January showed fractures of the 5th, 6th, 7th, and 8th left ribs and fractures of the 6th and 7th right ribs. Those on the right side were healed and had probably occurred several months or more before the fractures on the left side, all of which were recent fractures. She had suffered from a persistent cough for several years and could remember an attack with some pain in the right side much earlier in the year. The pain in the left side had started after a bout of coughing which had occurred when she was lifting some heavy washing. In both patients the fractures were antero-lateral.

Both these cases have one factor in common: the ribs were fractured when coughing occurred as the patient was bending—i.e., when the diaphragm was pushed up by the abdominal contents; they are in this respect similar to the cough fractures occurring in late pregnancy. In neither case did the patients show any radiological signs of either pulmonary tuberculosis or of any other abnormality of the ribs.

It is difficult to assess the incidence of bilateral cough fractures. The figure of 4% quoted by Bodenheimer is probably high, but it is certain that the condition is much commoner than the literature would suggest. It adds one further possibility to the list when the differential diagnosis of pain in the chest is being considered—and casts doubt on the diagnosis of "intercostal myalgia" or "fibrositis" when the pain is bilateral; in all respects the clinical features are similar to those found with unilateral fractures.

My thanks are due to the Librarian of the B.M.A. for his help with the references, and to Miss Marjorie Collins for secretarial assistance. Dr. C. B. Lanyon and Dr. J. Deighton kindly referred the patients to me.—I am, etc.,

Falmouth. P. E. S. PALMER.

REFERENCES

1 *British Medical Journal*, 1951, **2**, 1492.
2 Ibid., 1951, **2**, 1494.
3 *Amer. Rev. Tuberc.*, 1934, **30**, 566.
4 *J. Amer. med. Ass.*, 1936, **106**, 1543.
5 *Ann. intern. Med.*, 1945, **23**, 442.
6 *New Orleans med. surg. J.*, 1948, **100**, 474.

POINTS FROM LETTERS

Tetanus

Dr. K. M. HAY (Birmingham) writes: I have seen a case of tetanus recently in a young man which might be of interest. The patient pricked his finger on his wife's sewing about ten days before the onset of tetanus, but no blood was drawn. There was no other history of injury, nor had the patient ever suffered a severe laceration. Minor injuries of this sort are so common that it would be impossible to give antitoxin whenever they occur. . . . As things stand, it would seem that a doctor who fails to give serum in every case of injury, however trivial and whether blood is drawn or not, is likely to face considerable medico-legal trouble if tetanus should supervene, in spite of its rarity. The best solution would be for all the active members of the population to be immunized, as in the Services.

Dummies for "Air Babies"

Dr. MARY E. BUDDING (Tavistock) writes: Sir Harold E. Whittingham in Part I of his Refresher Course article (March 7, p. 556) on air travel makes a suggestion that mothers with babies should perhaps be instructed to give them a dummy to suck during ascent and descent. Perhaps unwittingly this might have the effect of once more increasing the sales of the undesirable dummy, which has at long last fallen into disrepute, even among mothers. . . . I myself have always appreciated the excellent brands of chewing-gum and peppermint ("extra strong") provided by the airlines, and wonder if Sir Harold Whittingham can use his influence to persuade them to provide our babies, when travelling, not with dummies, but perhaps with glycerin-based rapidly dissolved once-used-only large sweets?

Litigation Against Doctors

Dr. LESLIE HARTLEY (Camberley) writes: Under the new regulations a newly qualified doctor must take an appointment in a hospital. If he feels that the stigma of an action for damages against him may be attached to him at the very beginning of his career, the medical student may become as rare a bird as the infallible doctor. Actions such as these are bound to react ultimately on the public themselves, as medical men will refuse to take responsibility and will pass more and more work to the specialist if they feel that they are liable to be involved in litigation. A doctor friend of mine told me that when he got a foreign body underneath his upper eyelid in New York he had to put up with it for three hours before he could contact an ophthalmic surgeon to evert his lid and remove it, as no nurse or doctor would touch his eye. When he told the ophthalmic surgeon that any trained nurse or doctor in England would have done it for him, he said, "Ah, yes, but they do not litigate in your country." A High Court judge recently called attention to the increasing amount of litigation in this country since the introduction of free legal aid, which means that people can bring actions at the taxpayer's expense.

Misuse of Words

Dr. R. T. D. FITZGERALD (Eastbourne) writes: May I add to your collection of misused words two favourites from my own collection? In the days when doctors wrote English and congenital syphilis was rife it was not uncommon for patients to suffer from Hutchinson's triad, but now that doctors follow the artists in their search for novelty for novelty's sake, and write indifferent journalese and ambiguous jargon, congenital syphilis has given way to congenital heart disease and patients suffer from Fallot's tetralogy. Let us remember that, however interested we may be in Fallot's tetralogy, our patients can only suffer from Fallot's tetrad. The anthropoid pelvis has recently been so called from its resemblance to that of the ape, but it so happens that our learned fathers called the apes anthropoids from their resemblance to the human species.

A Coroner's Remarks

Dr. M. G. L. LUCAS (H.M. Coroner for the North District of the County of Bedford) writes: My attention has been called to the literature which accompanies a current advertisement of "persomnia." It quotes remarks made by the "Bedford Coroner" on September 23, 1952, and the suggestion is made in an accompanying letter from the medical director of Clinical Products, Ltd., that he is entitled to use the remarks of the "Bedford Coroner" as testimony of the advantages and safety of the tablets in question. I wish to make it clear that I did not take up office here until October 1, 1952. The verdict was not mine and I cannot associate myself with the opinions expressed.

Obituary

LEO DOYLE, M.B., M.S., F.R.A.C.S.

The sudden and unexpected death of Mr. Leo Doyle at the close of an operation which he had been performing at the Mercy Hospital, Melbourne, has robbed the Australian continent of one of its foremost surgeons. We are indebted to Sir Gordon Gordon-Taylor for the following appreciation:

Born in 1891, Leo Doyle graduated in medicine at the University of Melbourne in 1913, and served in the Royal Australian Navy in the 1914–18 war. He had belonged to the first batch of undergraduates who joined St. Vincent's Hospital when it became recognized by the University of Melbourne as a clinical school; he subsequently became its first registrar, and lived to be senior surgeon for a number of years to the hospital of his choice. Doyle was never afflicted with any *furor scribendi*, and his name is therefore less well known than some of his compatriot colleagues', save to those of this country to whom has been vouchsafed the privilege of visiting the great surgical centre of Melbourne and to the many young surgical aspirants in London and Britain to-day—a goodly proportion from "Vincent's"—by whom the name of Leo Doyle is respected and esteemed and to whom the man himself was a veritable surgical father.

Leo Doyle's repute will not rest upon his teaching, nor was he one "to be sought for in the council of the people": he was a man of few words, a flair for diagnosis, and a sharp knife—not that he contemned the diathermy, for there were some who regarded his diathermy gastrectomy for peptic ulcer, without the employment of clamps, as one of the very best examples of his superb surgical technique. He was never satisfied with himself, always wanting to do something better:

> Who, not content that former worth stand fast,
> Looks forward, persevering to the last,
> From well to better, daily self-surpast.

Like the artificer of Ecclesiasticus, he "set his heart upon perfecting his works, and he will be wakeful to adorn them perfectly," so that of Leo Doyle it may be truly said that he was *simplex munditiis*, a worker simple in his elegance.

I believe that most Australian surgeons would share the writer's view and acknowledge Doyle's supremacy in the operative treatment of malignant disease, and I have memories, on my many visits to Melbourne, of cases in his wards convalescing from operations as diverse as pharyngectomy, laryngectomy, pharyngo-laryngectomy, oesophagectomy, total gastrectomy, and the "hindquarter" amputation, of which he had done several. He was proud of having been house-surgeon to that great pioneer of thyroid surgery, Sir Thomas Dunhill, and never tired of expressing his indebtedness to his old chief. A true exemplar of Cromwell's hope—"To be a Seeker is to be of the best sect next to a Finder"—he remained a humble student to the end.

His home life was a happy one, and loyal assistants like Lorna Sisely and Ellery Ryan, who each remained with him for many years, virtually belonged to the family. Leo Doyle worthily maintained the prestige and lustre of a hospital which could boast of Dunhill and of Devine as having served on its staff, but by his intense humanity he also proved himself a true disciple of that

Father Vincent, dead nearly 300 years ago, whose name attaches to hospitals on either side of the Equator, but whose spirit and example pervade a far larger number who lack the title of "Vincent's." From the manner of his passing he was not destined to repine the dwindling activities of advancing years, when in the words of Adam Lindsay Gordon, whose statue finds a place only a few yards from Leo Doyle's hospitable home in Spring Street:

> The songs are ended, the deeds are done,
> There shall none of them gladden me now, not one,
> There is nothing good for me under the sun,
> But to perish, as these things perished.

Leo Doyle lived and died "the happy Warrior . . . that every man in arms should wish to be."

Mr. J. W. WALKER, who was well known in the West Riding as a surgeon and as an archaeologist, died at his home near Bristol on February 17 at the age of 93. John William Walker was born at Wakefield on October 15, 1859, the son of Thomas Walker, J.P., and was educated at Rossall School and at University College, London. After qualifying in 1882 he worked in London for a time and held appointments at University College Hospital. Later he settled in practice at Wakefield, where he became surgeon to the Clayton Hospital. During the war of 1914–18 he served in the R.A.M.C. at the 2nd Northern General Hospital at Leeds. For his war services he was appointed O.B.E. in 1920. Mr. Walker was admitted to the Fellowship of the Royal College of Surgeons of England in 1941, at the age of 81, as a Member of 20 years' standing, and thus joined his two sons, R. Milnes Walker, now professor of surgery in the University of Bristol, and J. H. Milnes Walker, of Crewe. He took a leading part in local affairs, being a J.P., a governor of Wakefield High School, and an honorary life member of the St. John Ambulance Association. But outside his profession his main interest was in local history. His association with the Yorkshire Archaeological Society, of which he was the oldest member, dated back to 1882, and in 1924 he was elected a vice-president, later becoming president. He was also a member of the council of the society and had been its records secretary. The Wakefield Historical Society also paid him the honour of electing him its president. In his book, *Robin Hood Identified*, published in 1946, he endeavoured to prove that the Sherwood Forest outlaw was a certain Robert Hood, of Wakefield. He also wrote several other books and monographs, including *The Cathedral Church of Wakefield* (1888), *Handbook for Yorkshire* (1904), *The Church Plate of Berkshire* (1927), and *Wakefield, Its History and People*, a book which required a second edition in 1939. Mr. Walker retired from practice in 1921, and then lived in Berkshire, where he joined the Berkshire Archaeological Society and served on its council. After a move to Cheshire he finally settled at Churchill Court, near Bristol, where he died. He married Miss Constance E. Holdsworth, daughter of Samuel Holdsworth, J.P., in 1885, and in 1945 they had the satisfaction of celebrating their diamond wedding. Mr. Walker is survived by his two sons and two daughters.

By the death of Dr. J. G. BENNETT at his home at Woodley, Cheshire, on March 11 in his 64th year, the profession has lost a member of extensive experience, both as a general practitioner and as an officer in the public health service. John George Bennett was born on November 14, 1888, and he received his medical education at the University of Manchester, graduating M.B., Ch.B. in 1913, having gained the Tom Jones scholarship in anatomy and a distinction in medicine. His immediate postgraduate training included the holding of posts as house-surgeon at the Manchester Royal Infirmary and at Pendlebury Children's Hospital. He then entered the R.A.M.C. and served throughout the war of 1914–18, being sent first to France and then to India and Mesopotamia. For his services he was awarded the Military Cross in 1919. Upon his return to civil life he was appointed assistant lecturer in the anatomy and physiology department of Manchester University, and in 1920 he proceeded to the degree of M.D. after writing a thesis describing his investigations into the embryological and pathological relationships of the lesser sac in the newborn. He also served for a short period as chairman of a pensions board, for which his experience in tropical diseases was particularly valuable. In 1922 Dr. Bennett married Miss Kathleen Ward Siddell, and in the following year he began his career as a general practitioner at Hyde. His general good will towards his patients and his keen interest in their well-being soon enabled him to build up the extensive practice which he conducted for 17 years. During this stage of his career he was a complete success, being held in high regard both by his patients and by his professional colleagues who elected him chairman of the Hyde Division of the British Medical Association from 1937 to 1939. After many years of strenuous work he retired from general practice for reasons of health just before the last war. But when the need for medical men became so essential, he was eager to serve his country again and found scope for his enthusiasm by acting as a medical referee, as a member of the recruitment medical board at Stockport, and as chairman of the pensions board at Manchester. During the last nine years of his life he turned his attention to preventive medicine by accepting the appointment of assistant medical officer of health to the Borough of Hyde, where his work was that of a clinician in the maternity and child welfare and school medical field, and as deputy superintendent at the Hyde Isolation Hospital. With the inauguration of the National Health Service his post was redesignated as that of assistant county medical officer in Cheshire, an appointment which enabled him to continue in the same field of operations. His work in the public health service, like his earlier work as a general practitioner, was most impressive. He was a grand colleague and a good man, and his death has left his associates with a sense of personal loss. His last illness was of short duration, rendered more short through a great determination to remain at duty upon many occasions when most men would have taken the easier course of obtaining a much-needed rest. He died in harness, as seemed to be his intent. Apart from his work, Jack Bennett had a keen interest in gardening and in painting water colours, and he loved a day's shooting. He is survived by a widow and a daughter, Mrs. Mary Howard, wife of Dr. Brian Howard, and to them we offer our deepest sympathy. —F. W. C. B.

Dr. HERMAN BARUCH, a former United States Ambassador to the Netherlands and to Portugal, and brother of Mr. Bernard Baruch, the statesman, died in Long Island on March 15. Herman Benjamin Baruch was born on April 28, 1872, the son of Simon Baruch (1840–1921), a well-known surgeon. He qualified in medicine at Columbia University, New York, in 1895, and spent the next eight years in general practice. He forsook medicine for finance in 1903 when he joined the New York stock exchange as a member of the firm of Baruch Brothers. During the last war he was appointed special representative of the Board of Economic Warfare in Brazil and special economic adviser to the U.S. Ambassador to Brazil. From 1945 to 1947 he was U.S. Ambassador to Portugal, and from 1947 to 1949 Ambassador to the Netherlands. He then retired from the diplomatic service. He was president of the Simon Baruch Foundation (so named in honour of his father), and he devoted the last years of his life to directing the Foundation's research into the aetiology and treatment of poliomyelitis.

Medico-Legal

DRUNK IN CHARGE

BY

A. E. M. HARTLEY, M.B., B.Ch.

The examination of the alleged drunk in charge usually falls to the general practitioner. To many it is one of the nightmares of general practice. It occurs so seldom that occasionally the doctor is not prepared for it, and his examination at the time may be incomplete so far as the law is concerned. He may therefore be cross-examined at length both in the magistrates' court and later at the quarter sessions. Bitter experience of this has prompted me to compile the proforma below. If properly completed at the time of the examination it should ensure that the examining doctor is standing on firm ground at any subsequent cross-examination.

I have had a number of these proformas duplicated by the police, and they are kept at the police station. Whenever a case turns up, one of these forms is produced for me at the time and my notes are made on it. These I am allowed to produce in court. I submit this form in the hope that it may be of some use to those practitioners who see little of this type of medico-legal work, and also in the hope that anyone who can suggest any improvement to it will write to me. Is it too much to suggest that this or some similar form should be available at every police station in the country for the use of examining doctors? The spacing on the form allows for short notes to be made at the time.

OXFORDSHIRE CONSTABULARY

Examination at:
Date:
Time called: Time arrived:
Warning: (Tell him who you are and inform him that he is entitled to call his own doctor if he wishes. Obtain his consent to the examination.)
Name and address of person examined:

Essential Questions

1. Ask him date and time.
2. History for the day. (Note memory for recent events.)
3. What drinks? Type, amount, and time of consumption.
4. What food? When and where consumed? What did he eat?
5. Medical history:
   (*a*) Any serious illnesses. (Diabetes, heart, blackouts, epilepsy.)
   (*b*) Any recent illness.
   (*c*) Any operation.
   (*d*) Any deformity; spine or joints.
   (*e*) Any loss of member; arm, leg, eye.
   (*f*) Does he take drugs (1) habitually, (2) that day?
   (*g*) Is his eyesight normally good? Does he wear glasses?
   (*h*) Has he vomited?
   (*i*) Does he wear dentures? Are they in place?
   (*j*) Has he suffered any injury that day? Blow on head?

Examination

1. Take specimen of handwriting. Separate sheet to be used as exhibit.
2. Visual acuity. With glasses if worn.
   (*a*) Snellen's Types.
   (*b*) Newsprint.
3. Eyes:
   (*a*) Bloodshot.
   (*b*) State of pupils.
   (*c*) Reaction to light.
   (*d*) Accommodation.
   (*e*) Ocular movements.
4. Smell of breath:
   (*a*) Alcohol.
   (*b*) Disease.
5. State of tongue.
6. Teeth and throat.
7. Facies:
   (*a*) Flushed.
   (*b*) Pale.
   (*c*) Cyanosed.
   (*d*) Sweating.
8. General demeanour (abusive, hilarious, talkative, truculent).
   Disorder of dress.
   Signs of vomit.
9. Specimen of urine: albumin, sugar, blood, alcohol, or drugs.
10. Signs of shock.

General Medical Examination

1. Pulse: rate, character, rhythm.
2. Temperature.
3. Respirations; rate and type.
4. Blood pressure.
5. Heart: signs of disease.
6. Lungs: signs of disease.
7. Abdomen: scars or signs of disease.
8. Deformity or artificial limb or eye.
9. Scalp and head. Any injury, old or recent.

Special Tests for Co-ordination

1. Tip of nose test.
2. Romberg's test.
3. Walking a line.
4. Speech: mumbling, slow, indistinct, slurred, or shouting.
   Read short paragraph aloud.
   Simple spelling test.
5. Picking up coins:
   (*a*) Distinguish them.
   (*b*) Count number of coins.
   (*c*) Add to correct amount.

Opinion

Inform him of your opinion at the time and tell him again that he is entitled to call his own doctor.

Note.—See that the examination is carried out in a quiet room with good light and always in the presence of a police officer.

Medical Notes in Parliament

Smoking and Cancer

Mr. HARRY HYND used the adjournment motion in the House of Commons on March 19 to discuss the relationship between smoking and lung cancer, and to seek some authoritative pronouncement from the Ministry of Health on the subject.

He based his argument on the investigations carried out by Dr. Richard Doll and Professor Bradford Hill, whose reports in 1950 and December, 1952, were published in the *British Medical Journal*, and quoted the comment of the *British Medical Journal* (December 13, 1952, p. 1299) in a leading article: "Tobacco has been incriminated as the vehicle conveying an agent responsible for a large proportion of the cases. Out of any random sample of 400 men now aged about 55, at least 10 must be expected to die of cancer of the lung within the next 20 years. Intensive research on the chemical constituents of tobacco and tobacco smoke is now needed." This, Mr. Hynd said, was bad enough, but similar investigations in Germany and the U.S. had led to similar conclusions. The stage had been reached when the medical profession must make up its mind about the cause of this dread disease, and whether it really was related to smoking; and it was part of the responsibilities of the Ministry of Health to guide the public in these matters.

Miss HORNSBY-SMITH, Parliamentary Secretary to the Ministry of Health, acknowledged that the subject was one of great public concern, and quoted from the 1950 report of the Chief Medical Officer of the Ministry that "cancer, and especially cancer of the lung, remains the greatest problem of medicine." But the figures given by Mr. Hynd of the rise in the number of cases of cancer of the lung from 2,281 in 1931 to 13,247 in 1951 must be qualified by taking account of the vastly improved diagnosis, the universal use of *x* rays, and the increased education of prac-

titioners on cancer work which had taken place during those 20 years. In view of the gravity of the statistical evidence the Ministry and the Medical Research Council were examining carefully what lines of research into the incidence and causative factors were most promising and should be encouraged, and had also taken the initiative in stimulating new lines of research.

The information so far received from the advisory committee of the Medical Research Council showed that, while it accepted that research had shown a statistical relationship between tobacco smoking and lung cancer, it did not necessarily accept that that relationship meant a causal relationship also.

She gave a résumé of the research activity that was in progress. An example of the new lines of research was the experiments in nuclear physics. A new cobalt-60 beam unit, a generous gift from Canada, had been accepted a few days previously by the British Empire Cancer Campaign (see *Journal*, March 21, pp. 666 and 669). In the N.H.S. hospitals there was intensive research. It was going on in the Royal Cancer Hospital and the Chester Beatty Research Institute, the Christie Hospital and the Holt Radium Institute, and in the Hammersmith Hospital, where some of the most modern equipment was being used to find a new means of diagnosis and cure. At St. Bartholomew's Hospital Sir Ernest Kennaway was examining the ingredients of tobacco smoke for cancer-producing substances. At the Pneumoconiosis Research Institute in Cardiff the Medical Research Council was carrying out experiments on the effect on mice of living for long periods in tobacco smoke. At the cancer research unit of the Royal Beaston Memorial Hospital in Glasgow further extensive research was in progress into cancer-producing agents, again related to tobacco smoke, and the possible carcinogenicity of alkaloids in tobacco or its smoke. Similar research was being conducted in America. Fortunately there was no iron curtain in research on this subject, and the best brains throughout the world were co-ordinating their work. In regard to atmospheric pollution and its relation to cancer of the lung, Dr. Percy Stocks was conducting an investigation for the Medical Research Council. The difference between the incidence of cancer of the lung in rural areas and in densely populated industrial areas was dramatic. All the evidence so far on the arsenic content of some tobaccos as a causation of lung cancer showed that the amount was too small to be effective in carcinoma.

She concluded that they must see that nothing was done to panic the public, while assuring them that everything was being done to find a cure for this disease. Research had not been abandoned into exhaust gases from petrol and diesel engines as a possible source contributing to lung cancer. The Ministry's attitude was that it could act only on the best medical advice available, and while the advisory committee had not come to any conclusion going beyond the correlation between tobacco smoke and cancer of the lung the Ministry could only be non-committal. Research was proceeding all the time. It was a long-term matter requiring careful sifting of results and highly complicated experimental work over a long period and the collection of vital statistical data.

The Medical Research Council would have no hesitation in carrying further research into any line which showed promise, and would do everything in its power to find a solution and a cure of this dread disease.

Group Practices

Mr. HILARY MARQUAND on March 19 asked the Minister of Health whether he had drawn the attention of executive councils and their medical committees to the fact that both he and the General Medical Services Committee had accepted the encouragement of group practice as a desirable objective. Mr. IAIN MACLEOD replied that he had received advice from the Central Health Services Council on the definition of group practice, and proposed shortly to discuss with representatives of the medical profession how best to implement the recommendation on group practice of the Working Party on the distribution of remuneration of general practitioners. He added that he had received the report only the previous night, and he would consider what publicity should be given to the committee's conclusions.

Medical Auxiliaries

Mr. M. TURNER-SAMUELS asked the Minister of Health on March 19 if he would make a statement at an early date on the implementation or otherwise of the Cope Report. Mr. IAIN MACLEOD stated that, following discussions with the professional bodies of medical auxiliaries, the Secretary of State for Scotland and he were satisfied that there was insufficient agreement on fundamental matters to proceed with statutory registration on the lines proposed by the Cope Committees. They intended, therefore, as soon as possible to make regulations using the power of Section 66 of the National Health Service Act, 1946, and Section 65 of the National Health Service (Scotland) Act, 1947, to prescribe qualifications for medical auxiliaries for the purpose of employment in the National Health Service. They would shortly give the professional and other bodies concerned an opportunity to comment on an outline of the regulations proposed. He added that he intended when making the regulations to withdraw the temporary instructions given in August, 1951. He would do everything he could to see that the regulations he proposed were fair to all the associations concerned.

Sickness in the Post Office

Mr. C. OSBORNE asked the Assistant Postmaster-General on March 18 what had been the sick rate amongst Post Office employees in terms of days' absence per person for the years 1952 and 1951, and how this compared with the pre-war figure. Mr. L. D. GAMMANS informed him that the average number of days' sick absence per person for non-disabled established staff was as follows : In 1938, 8.1 days for men and 9.3 for women ; in 1951, 15.0 days for men and 18.4 for women. The corresponding figures for 1952 were not yet available. Mr. Gammans added that successive administrations had been disturbed about this alarming increase. It was estimated that if the figures were the same as before the war there would be a saving in staff of at least 6,500. Before the war the Post Office had its own doctors, whereas now the staff came under the National Health Service. He also said that the matter was under careful consideration in co-operation with the trade unions.

Prescription Costs

Mr. A. BLENKINSOP on March 19 asked the Minister of Health what was the estimated average number of prescriptions on each form and the average cost of each prescription at the latest available date, and how these figures compared with those before the introduction of the prescription charge. Miss PAT HORNSBY-SMITH replied that in England and Wales the estimated average number per form was 1.71 in February, 1953, 1.57 in May, 1952, and 1.59 in February, 1952. The estimated average cost was about 4s. 2½d. in December, 1952, compared with an average cost of 4s. 1¼d. in May, 1952, and 3s. 10½d. in December, 1951.

Mr. BLENKINSOP suggested that the figures implied that the prescription charge had added to the cost per prescription in many cases, and had encouraged doctors, for understandable reasons, to add to the amount of drugs prescribed, and thereby increased considerably the amount of wastage. Miss HORNSBY-SMITH said the Minister could not accept that as the sole explanation. The main cause was increasing prescribing and expensive new drugs.

Mr. LESLIE HALE asked the Minister of Health on March 17 what was the estimated total net saving to the Exchequer, after making allowances for administrative costs and for the extra cost to the National Assistance Board, both direct and administrative, of the charge of 1s. on prescriptions from the time of its introduction to the nearest most convenient date for computation.

Mr. IAIN MACLEOD replied that the estimated net saving to the Exchequer from the prescription charges paid by patients in England and Wales between June 1 and

December 31, 1952, after the deduction of refunds made by the National Assistance Board, was about £2¼m. Administrative costs, though not known in detail, would not materially affect this estimate. In addition there was a saving to the Exchequer during this period of about £1¼m. because fewer prescriptions were dispensed than would have been expected if charges had not been introduced, though it was possible that other factors contributed to this decrease.

Doctors' Surgeries

Mr. A. BLENKINSOP on March 19 asked the Minister of Health what action he was taking to secure an improvement in the condition and equipment of general practitioners' surgeries. Dr. SANTO JEGER also asked the Minister what regulations he had made on the standard of surgery and waiting-room accommodation in doctors' premises under the National Health Service, how many had been inspected by executive councils, and how many had been declared unsuitable.

Miss PAT HORNSBY-SMITH, the Parliamentary Secretary, informed them that the relevant regulation was paragraph 7(4) and (5) of Part I of the First Schedule to Statutory Instrument 1948, No. 506. The Minister had no details of inspections by executive councils. He was, however, hoping shortly to discuss the best way of securing an improvement, where necessary, in the condition and equipment of general practitioners' surgeries and waiting-rooms with representatives of the medical profession.

Provision for Mental Hospitals

Mr. KENNETH ROBINSON asked the Minister of Health on March 19 what special capital allocation he was making for the coming financial year to meet the needs of the mental hospitals.

Mr. IAIN MACLEOD stated that it was for regional hospital boards to decide what particular projects should be included in their capital programmes, but he had again asked them to devote at least 20% of their allocations to mental health projects. In addition, two major mental health schemes were being financed from a special central reserve.

Mr. ROBINSON insisted that 20% was quite insufficient. Mr. MACLEOD agreed that this was probably the most serious problem facing the National Health Service, and it was precisely for that reason that he had insisted on the minimum figure he had given. The position would have been a great deal easier if in the first year or two of the Service a larger proportion of the resources had been devoted to mental health purposes.

Students' Suicides

Lieutenant-Colonel M. LIPTON on March 19 asked the Minister of Health whether he would appoint a committee of medical and other experts to investigate the high number of suicides in recent years among schoolboys and undergraduates. Mr. IAIN MACLEOD replied that the figures for suicides among boys between 10 and 14 were too small to be statistically significant. Separate figures for older students were not available. He was, however, aware of the concern about this problem, and, while he did not think it would be appropriate for him to set up a special committee, he was sure the problem would be carefully watched by all concerned.

He said in a further reply that the general suicide rate for boys and men between 15 and 24 was lower than the general rate and had been falling in recent years. The fullest facilities were available to universities for dealing with the general problem, and he thought the matter was best left to them. If they asked for his help he would be delighted to assist.

The Committee on the Disabled set up by the Ministers of Labour and Health and the Secretary of State for Scotland has two medical men as members, Sir Claude Frankau and Dr. C. G. Magee.

Help for Disabled.—Sixty-five local authorities in England and Wales have submitted schemes for promoting the welfare of physically handicapped persons. Other schemes are still coming in, and the Minister of Health does not propose to issue directions to authorities yet.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **March 7** (No. 9) and corresponding week 1952.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1953 Eng & Wales	1953 Lond.	1953 Scot.	1953 N. Ire.	1953 Eire	1952 Eng & Wales	1952 Lond.	1952 Scot.	1952 N. Ire.	1952 Eire
Diphtheria	22	1	8	0	4	33	2	24	0	1
Dysentery	289	39	97	0	5	647	82	82	10	
Encephalitis, acute	8	1	0	0		3	2	0	0	
Enteric fever:										
Typhoid	6	1	1	0		4	2	0	0	2
Paratyphoid	6	0	0	0		12	0	1(B)	0	
Food-poisoning	183	24		0		74	13		0	
Infective enteritis or diarrhoea under 2 years				9	24				12	16
Measles*	27,638	1621	465	135	369	6,233	153	512	192	158
Meningococcal infection	35	6	17	1	2	34	3	24	4	5
Ophthalmia neonatorum	42	3	7	0		31	1	9	0	
Pneumonia†	1,301	55	387	21	23	1,061	36	544	20	3
Poliomyelitis, acute:										
Paralytic	12	1	3	0	4	15	0	1	0	1
Non-paralytic	5	0				4	1			
Puerperal fever§	265	55	11	2		274	40	14	2	1
Scarlet fever	1,534	83	202	32	58	1,506	153	229	19	71
Tuberculosis:										
Respiratory			157	31				171	32	
Non-respiratory			33	3				36	2	
Whooping-cough	2,758	187	278	26	87	2,789	116	252	106	42

DEATHS in Great Towns	1953 Eng & Wales	1953 Lond.	1953 Scot.	1953 N. Ire.	1953 Eire	1952 Eng & Wales	1952 Lond.	1952 Scot.	1952 N. Ire.	1952 Eire
Diphtheria	1	0	1	0	0	0	0		0	0
Dysentery	2	0		0		0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0	0		0	0		0	
Infective enteritis or diarrhoea under 2 years	15	6	4	2	1	15		0	0	0
Influenza	193	19	10	3	5	49	3	18	0	0
Measles		0	1	0	0		0		0	0
Meningococcal infection		0	0				1			
Pneumonia	469	72	28	17	9	354	48		14	19
Poliomyelitis, acute	2	0			0	1	0			0
Scarlet fever		0	0	0	0		0		0	0
Tuberculosis:										
Respiratory	134	10	16	2	7	170	30	32	3	17
Non-respiratory		4	3	2	0		3	4	0	2
Whooping-cough	3	0	2	0	0	0	0	1	0	0
Deaths 0–1 year	244	25	24	14	18	278	31	39	17	28
Deaths (excluding stillbirths)	6,706	915	721	159	207	6,630	975	739	150	238
LIVE BIRTHS	7,861	1173	864	197	485	7,756	1136	875	224	391
STILLBIRTHS	199	23	27			220	16	28		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Smallpox in the North Country

The outbreak of smallpox which began earlier this month in Todmorden M.B. (Yorkshire, West Riding) and Bacup M.B. (Lancashire)—see last week's *Journal* (p. 682)—is continuing. Up to March 23 11 cases have been diagnosed. The districts affected are as follows:

TODMORDEN M.B.

There have been 9 cases with 1 death (on March 20). In addition to the 3 cases mentioned last week there have been 6 more secondary cases, all in the two households originally involved. These 6 patients were all under surveillance when they sickened and were promptly removed to hospital. Details of these cases are as follows:

Case 5. Female aged 13, daughter of Case 1. Unvaccinated until March 13. Illness began on March 17, and she was admitted to hospital on the following day. The rash appeared on March 20.

Case 6. Female aged 40, wife of Case 1. Vaccinated in infancy and revaccinated on March 13. Onset of illness on March 19 and admitted to hospital on that day. The rash appeared on March 20.

Case 7. Female aged 35. Lodged with Cases 2 and 3. Unvaccinated. Primary vaccination on March 15 and revaccinated on March 18. Onset of illness March 19 and admitted to hospital same day.

Case 8. Male, 19, son of Cases 2 and 3. Unvaccinated. Primary vaccination on March 15. Onset of illness on March 19 and admitted to hospital same day.

Case 9. Male, 14, son of Cases 2 and 3. Unvaccinated. Primary vaccination on March 15. Onset of illness March 19 and admitted to hospital same day.

Case 11. Male, 53. Contact with Case 1 for 30 minutes on March 11. Vaccinated in infancy and during 1914–18 war. Revaccinated on March 13. Onset of illness on March 21 and admitted to hospital on the following day.

BACUP M.B.

There have been no further cases since the first case reported last week. This patient died on March 13 in the Florence Nightingale Hospital, Bury C.B., and there have been no reports of illness among contacts under surveillance at Bury.

OLDHAM C.B.

An unvaccinated man of 26 living in this district and working as a cotton operative at Hollingwood, Chadderton M.B., fell ill on March 13. A rash developed on March 18 and he was admitted to hospital with smallpox on March 20 (Case 10). So far no human link with the other cases has been found. The mill in which this man worked may have received cotton waste or part of a consignment of raw cotton from the Todmorden mill at which the first 3 patients were employed, but it is too soon to say whether or not an extra-human source of infection is involved. This patient was living in a lodging-house in Oldham and unprotected contacts are numerous.

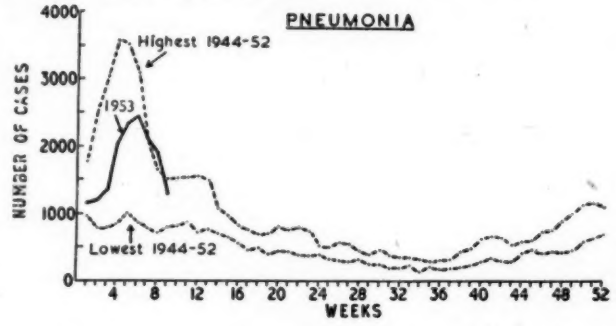
Of the 9 patients at present in hospital 2 are recovering and 3 are seriously ill. Eight are in the Oakwell Smallpox Hospital and 1 is in hospital at Ainsworth, near Bury. So far there are no reports of illness among contacts under surveillance at Halifax. The first of the Todmorden patients was originally admitted to the Halifax General Hospital.

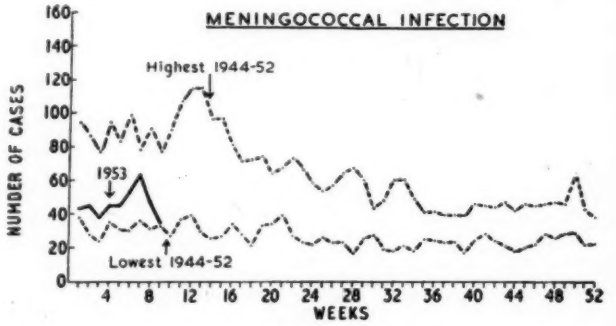
Week Ending March 14

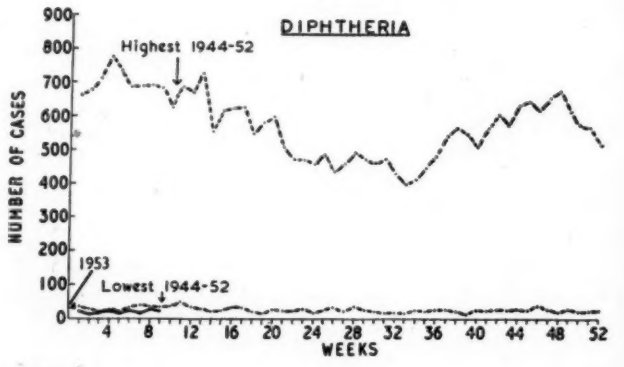
The notifications of infectious diseases in England and Wales during the week included scarlet fever 1,675, whooping-cough 3,072, diphtheria 31, measles 26,924, acute poliomyelitis 17, dysentery 362, paratyphoid fever 6, and typhoid fever 1.

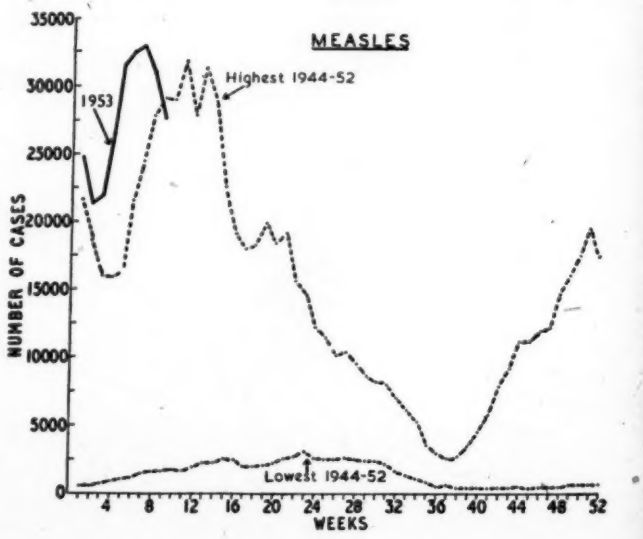
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1944–52 are shown thus - - - - - - -, the figures for 1953 thus ————. Except for the curves showing notifications in 1953, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

The only large variations in the trends of infectious diseases in England and Wales during the week ending March 7 were falls of 3,246 in the notifications of measles, from 30,884 to 27,638, 596 for acute pneumonia, from 1,897 to 1,301, and a rise of 79 for scarlet fever, from 1,455 to 1,534.

The largest decline in the number of notifications of measles was 374 in Lancashire, from 1,829 to 1,455. In seven other counties a decrease of over 200 was recorded. Only small variations were recorded in the local trends of scarlet fever. The notifications of whooping-cough were 12 more than in the preceding week, rising from 2,746 to 2,758. With the exception of a fall of 145 in Lancashire, from 682 to 537, only small fluctuations occurred in the local trends of whooping-cough. 22 cases of diphtheria were notified during the week, being 5 fewer than in the previous week. The chief feature of the returns for diphtheria was a decline from 4 to 1 in both the counties of Devonshire and Warwickshire. The largest falls in acute pneumonia were 78 in Warwickshire, from 155 to 82, and 58 in Middlesex, from 104 to 46.

17 cases of acute poliomyelitis were notified during the week. Paralytic cases numbered the same and non-paralytic cases 4 more than in the preceding week. 3 cases were notified in the counties of Surrey and Huntingdon.

The notifications of dysentery, 289, were 37 more than in the preceding week. This rise was mainly due to an increase of 33 in Lancashire, from 58 to 91. The chief centres of infection in this county were Preston R.D. 53 and Liverpool C.B. 22. The other large returns were London 39 and Yorkshire West Riding 23 (Leeds C.B. 11). Only 5 cases of dysentery were notified during the week in Grimsby C.B., where 533 cases have been reported since September.

193 deaths from influenza were registered in the great towns, 120 fewer than in the previous week.

Medical News

Local Medical Societies.—Recent meetings have included the following: *Manchester Medical Society.*—On February 4 Dr. J. H. Kellgren opened a discussion in the section of medicine on "Clinical Uses of Cortisone and A.C.T.H." He was followed by Dr. S. Oleesky, and by Mr. A. S. Scott, who considered ophthalmic conditions. On February 5 Dr. R. G. Gordon Jones read a paper to the section of anaesthetics on "Epidural Anaesthesia." Multiple paravertebral blocks, he said, could be produced with a single injection of local analgesic into the epidural space. The solution escaped through the intervertebral foraminae into the paravertebral spaces, where it produced its effect on the spinal nerves. Dr. P. D. Kelsall followed with a paper on anaesthesia for bronchoscopy, and Dr. J. P. Payne with one on arteriotomy in neurosurgery. On February 25 Dr. C. M. Fletcher read a paper to the section of medicine on research into occupational dust disease, discussing the investigations carried out by the Medical Research Council's Pneumoconiosis Research Unit since it was set up in 1945. He said that two outstanding lessons had been learned: (1) the great importance of observer error in all clinical and radiological estimates of the severity of any disease; (2) the distorted picture of the prevalence and the severity of a disease given by a hospital population compared with those affected by the same disease outside hospitals. *Liverpool Medical Institution.*—At a meeting on February 19 Dr. J. Berkson discussed "Oxygen, the Premature Baby, and Retrolental Fibroplasia." He suggested that as oxygen was a drug with certain toxic effects it should be given only in the lowest concentration required by the particular patient. The discussion was continued by Mr. A. McKie Reid and Dr. E. Dunsby. Mr. A. Sutcliffe Kerr then read a paper on "Unilateral Proptosis." *Chelsea Clinical Society.*—The sixth meeting of the 56th session was held on March 10 with the president, Mr. Eric Steeler, in the chair. A discussion on "The Medical Aspects of Road Accidents" was opened by Mr. K. L. Kelly, deputy secretary of the Automobile Association, and was continued by Sir Hugh Griffiths and Drs. L. G. Norman, David Matthews, Simpson Harvey, Skene Keith, and Brunton Blaikie. The date of the annual dinner was announced for May 12.

Sport and Medicine.—The British Association of Sport and Medicine had its first general meeting on February 27, with Sir Arthur Porritt in the chair. The president, Sir Adolphe Abrahams, told the meeting that the association had been founded with the aim of making it the authoritative body on every medical aspect of athletics and exercise. It would advise on all the general principles of athletic training and on the various medical conditions which would and would not prohibit participation in sport. It would have to study the inevitable injuries of sport and its dangers, with particular reference to such problems as the effect of violent exercise during the incubation period of poliomyelitis and other infections, and the dangers of boxing, since so many fatalities in the ring had given rise to some alarm. Research would play an important part in the association's activities, and he hoped that this would break new ground—as, for example, the biopsy of the muscles of athletes.

Family Doctor.—A wide variety of interests are catered for in the April issue of *Family Doctor*, which is now on sale. The opening article presents the facts about smoking and health fairly and squarely: the reader can draw his own conclusions from them. Other informative and helpful articles are about the eyes (by Professor A. M. Low), tuberculosis (by Dr. Harley Williams), the chemistry of life (by Dr. J. Gordon Cook), accidents to children (by Professor John Craig and Dr. M. S. Fraser), toothpastes (by Mr. A. B. MacGregor), and "good health" (by Dr. Cuthbert Dukes). As usual there are a number of articles of special interest to mothers, besides the popular features—such as "Expert Advice," "Beauty and Health," "Family Doctor Speaking"—which now have an established place in the magazine. On nearly every page of the April issue there is useful information on subjects, of one sort or another, about which patients are so often inclined to ask questions of their doctor.

Faculty of Anaesthetists.—The Dean, Dr. Bernard Johnson, presided at the fifth anniversary dinner of the Faculty which was held at the Royal College of Surgeons on March 18. The Minister of Health, Mr. Iain Macleod, proposed the toast of "The Faculty," and drew attention to the great advances made in the art of anaesthesia. Anaesthesia, he said, was no longer the handmaiden of surgery but a true partner. The Dean, replying, referred to the great value of postgraduate teaching in anaesthetics in Britain. He announced that £5,000 had been given to the Faculty by John Wyeth & Brother to be used as scholarships for any overseas students in need of financial assistance. Dr. Johnson made a plea for a research department in anaesthesia which would be free from any other demands on its time. The toast of "The Guests," proposed by Dr. T. Cecil Gray, vice-dean of the Faculty, was acknowledged by Mr. A. A. Gemmell, P.R.C.O.G., and Mr. L. Farrer-Brown, secretary of the Nuffield Foundation.

Aetiology of Rheumatoid Arthritis.—A few copies of *The Aetiological Factors Associated With Rheumatoid Arthritis*, a report of the Empire Rheumatism Council Scientific Advisory Committee, are still available at the original price of 7s. 6d. It was published as a supplement to the *Annals of the Rheumatic Diseases.* Copies may be had on application to the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1. The report was prepared under the supervision of Dr. E. Lewis-Faning, statistician to the department of preventive medicine in the University of Wales. It is arranged in two parts—aetiological factors and clinical

pattern. The conclusions are based on a total of 532 questionaries completed at nine centres in England and Scotland, each patient being paired with a control subject of similar age, sex, and marital status. Other investigations carried out on large series of arthritic patients in Great Britain and abroad may usefully be compared with this national undertaking.

COMING EVENTS

Wessex Rahere Club.—The Spring Dinner of the Wessex Rahere Club will take place at the Castle Hotel, Taunton, on April 18. Further details may be obtained from the hon. secretary, Mr. A. Daunt Bateman, 3, The Circus, Bath.

British Association of Physical Medicine.—Annual meeting at University College Hospital Medical School, Gower Street, London, W.C.1, on April 17–18, 10.30 a.m. to 4.30 p.m. Lunch available each day (5s. 6d.). Annual dinner at Royal College of Surgeons on the Friday (tickets 35s.). Tickets must be applied for by April 4.

The Biochemical Society.—The 317th Meeting of the Biochemical Society will be a joint meeting with the Société Belge de Biochimie and will be held in the Faculty of Medicine, Brussels University, 115, Boulevard de Waterloo, Brussels, at 9 a.m. on April 11, when scientific papers will be read.

NEW ISSUES

Thorax.—The next issue (Vol. 8, No. 1) will be available in a week's time. The contents include:

A STUDY OF THE ORIGIN AND DEVELOPMENT OF LUNG CANCER. C. Raeburn and H. Spencer.
CARCINOMATOUS ABSCESS OF THE LUNG. C. Strang and J. A. Simpson.
CERTAIN UNUSUAL RADIOLOGICAL APPEARANCES IN THE CHEST OF COAL-MINERS SUFFERING FROM RHEUMATOID ARTHRITIS. Anthony Caplan.
THE PHYSIOLOGICAL BASIS OF REFLUX OESOPHAGITIS IN SLIDING HIATAL DIAPHRAGMATIC HERNIA. John A. Aylwin.
THE BRONCHIAL ARTERIES IN PULMONARY EMPHYSEMA. L. Cudkowicz and J. B. Armstrong.
FARMER'S LUNG: A REVIEW OF PRESENT KNOWLEDGE. C. J. Fuller.
ANOMALOUS PULMONARY VENOUS DRAINAGE. Alan R. Muir.
THE INFLUENCE OF STREPTOMYCIN ON THE INCIDENCE OF PLEURAL EFFUSION COMPLICATING THE DIVISION OF ADHESIONS. D. C. Beatty and A. Wiener.
A PRACTICAL MEASURE OF THE MAXIMUM VENTILATORY CAPACITY IN HEALTH AND DISEASE. M. C. S. Kennedy.

Published quarterly; annual subscription £2 2s., single copy 12s. 6d.

Annals of the Rheumatic Diseases.—The next issue (Vol. 12, No. 1) will be available in a week's time. The contents include:

RHEUMATIC COMPLAINTS IN AN URBAN POPULATION. J. H. Kellgren, J. S. Lawrence, and Jean Aitken-Swan.
INTRAVENOUS COLCHICINE IN THE MANAGEMENT OF GOUTY ARTHRITIS. W. Graham and J. B. Roberts.
CLINICAL STUDIES OF PHENYLBUTAZONE (BUTAZOLIDIN) AND BUTAPYRIN IN RHEUMATOID ARTHRITIS, RHEUMATOID SPONDYLITIS, AND GOUT. E. G. Kidd, K. C. Boyce, and R. H. Preyberg.
RADIOTHERAPY IN ARTHRITIS. M. H. L. Desmarais.
GOLD, SODIUM, AND LIVER FUNCTION IN RHEUMATOID ARTHRITIS. G. D. Kersley, L. Mandel, and M. R. Jeffrey.
RHEUMATOID ARTHRITIS TREATED WITH "IRGAPYRIN." ANALYSIS OF TWENTY CASES. G. Achari, B. Mukopadhaya, and P. Sengupta.
PROSEPTASINE IN THE TREATMENT OF RHEUMATOID ARTHRITIS. L. J. Barford.
EFFECT OF AN ANTIHISTAMINE IN RHEUMATOID ARTHRITIS. D. C. Wilson.
MARIE-STRÜMPELL SPONDYLITIS IN WOMEN. T. Lloyd Tyson, W. A. L. Thompson, and Charles Ragan.
EFFECTS OF ACTH ON THE PERIPHERAL BLOOD FLOW IN RHEUMATOID ARTHRITIS. J. W. Beattie and A. Woodmansey.

Issued quarterly; annual subscription £2 2s., single copy 12s. 6d.

These journals are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, March 30

●HUNTERIAN SOCIETY.—At Talbot Restaurant, 7 for 7.30 p.m., dinner meeting. Discussion to be opened by Dr. Keith Simpson, Dr. Robert Forbes, and Mr. D. C. Norris: Professional Pitfalls.
ROYAL EYE HOSPITAL.—5.15 p.m., Dr. T. H. Whittington: Myopia and the Care of the Myopic Patient.

Tuesday, March 31

●INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. D. F. O'Neill: Diagnosis and Management of Stress Disorders of the Skin.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor F. A. Henley: Gastrectomy with Replacement.

Wednesday, April 1

INSTITUTE OF UROLOGY.—At St. Paul's Hospital, W.C., 4.30 for 5 p.m., Dr. W. N. Mascall: Diagnosis and Treatment of Gonorrhoea.

APPOINTMENTS

COLLINS, MICHAEL JOSEPH, M.B., B.Ch., D.P.H., Deputy Medical Officer of Health, County Borough of Doncaster.

EAST ANGLIAN REGIONAL HOSPITAL BOARD.—R. Lindsay, M.B., Ch.B., Anaesthetic Registrar, Norfolk and Norwich Hospital; Alice M. Creamer, M.B., B.Ch., D.P.H., D.P.M., Registrar in Psychiatry, Fulbourn Mental Hospital and Psychiatric Department, Addenbrooke's Hospital; J. Littlejohn, L.R.C.P.&S.Ed., Registrar in Psychiatry, Fulbourn Mental Hospital; P. R. B. Noel, M.B., B.S., Medical Registrar, East Suffolk and Ipswich Hospital and Ipswich Borough General Hospital; D. J. Brewer, M.B., B.S., Medical Registrar, Foxhall Hospital, Ipswich; P. H. Cima, M.B., B.S., Medical Registrar, North Cambridgeshire Hospital and Clarkson Hospital, Wisbech.

HALL, T. S., M.D., D.P.H., D.Obst.R.C.O.G., County Medical Officer of Health and School Medical Officer, Shropshire County Council.

HELLER, ARTHUR DAVID, M.D., D.P.M., Assistant Psychiatrist, Deputy Medical Superintendent (Senior Hospital Medical Officer), Prudhoe and Monkton Hospital, Northumberland.

LAIDLAW, ALLAN JAMES, L.R.C.P.&S.Ed., L.R.F.P.S., Police Surgeon, City of Worcester.

NORTH-EAST METROPOLITAN REGIONAL HOSPITAL BOARD.—The following consultant appointments at the hospitals indicated in parentheses are announced: F. E. McLaughlin, L.R.C.P.&S.I., D.O.M.S., Part-time Ophthalmic Surgeon (Tilbury and Riverside); W. A. Hamer, M.B., B.S., F.R.C.S., Part-time Surgeon, and H. A. Pearce, M.B., B.S., F.R.C.S., Part-time Orthopaedic Surgeon (South-east Essex Group of Hospitals); J. N. T. Hutton, M.B., B.S., D.A., and H. R. Blades, M.R.C.S., L.R.C.P., D.A., Part-time Anaesthetists (St. Leonard's and St. Matthew's); Elizabeth H. Milne, M.B., Ch.B., D.A., Part-time Anaesthetist, St. Margaret's Hospital, Epping; Elizabeth D. S. Stephen, M.B., Ch.B., D.A., Part-time Anaesthetist, Broomfield Hospital, near Chelmsford; L. Citron, M.B., B.S., F.R.C.S., D.L.O., Part-time Ear, Nose, and Throat Surgeon, Chase Farm and other hospitals in Enfield Group; C. S. Savage, F.R.C.S., Part-time Ear, Nose, and Throat Surgeon, Southend-on-Sea Group of Hospitals; D. C. Arnott, M.B., B.S., D.C.H., D.Phys.Med., Part-time Physician in Physical Medicine, Queen Elizabeth Hospital for Children, London, E.

WARWICK, ELSPETH MARGARET, M.B., Ch.B., D.P.H., Deputy Medical Officer of Health, County Borough of Nottingham.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Brearley.—On March 17, 1953, at Mill Road Hospital, Liverpool, to Joyce Mary (formerly Hewitt) and Roger Brearley, F.R.C.S., of 55, Meadow Lane, West Derby, Liverpool, a son.
Green.—On March 7, 1953, to Dr. Elizabeth (formerly White), wife of Dr. D. M. Green, 3, Coupar Angus Road, Dundee, a daughter.
Jackson.—On March 15, 1953, at Glasgow, to Barbara, wife of C. R. S. Jackson, F.R.C.S., a son.
McCraith.—On March 18, 1953, at Freedom Fields Hospital, Plymouth, to Isabel (formerly McDonald), wife of Dr. John Anthony McCraith, a son—Nicholas Stuart.
Power.—On March 19, 1953, at Radley Lodge, Wimbledon, London, S.W., to Joy (formerly Parkes), wife of Dr. Norman Power, a second son.

MARRIAGES

Newns—Christmas.—On February 28, 1953, in Norwich, Norfolk, George Reginald Newns, M.B., M.R.C.P., to Patricia Mary Christmas, M.C.S.P.
Straschnov—Hodgson.—On March 26, 1953, at St. Hilda's Church, York, George J. Straschnov, M.R.C.S., L.R.C.P., R.A.F., St. Eval, Cornwall, to Pauline M. Hodgson, S.R.N., of 25, Millfield Lane, Hull Road, York.

DEATHS

Bartholomew.—On March 2, 1953, in a nursing-home, Francis Bartholomew, F.R.C.S.Ed., of Khartum, Sudan.
Fielding.—On February 17, 1953, at Keisall, Cheshire, Charles Robert Fielding, M.B., Ch.B., aged 56.
Horne.—On March 7, 1953, Walter Jobson Horne, M.D., M.R.C.P., of Highlands, Mereworth, Kent, formerly of Harley Street, London, W., aged 87.
Hutchinson.—On March 4, 1953, at Laverstock Nursing Home, Kingswood Road, Tunbridge Wells, Kent, Samuel Hutchinson, M.R.C.S., L.R.C.P., Hon. D.A., aged 70.
Lewellyn.—On February 25, 1953, at Manor Farm, Sutton Mandeville, Wilts, John Woodruff Lewellyn, M.R.C.S., L.R.C.P., formerly of Kingswood, Bristol, aged 74.
Lomax.—On March 6, 1953, at the Royal Infirmary, Liverpool, Harold Aloysius Lomax, M.B., Ch.B., J.P., of Bute House, St. Helens, Lancs.
McBean.—On March 3, 1953, at 352, Upper Richmond Road, Putney, London, S.W., Samuel Leslie McBean, M.B., B.S., aged 70.
MacDonald.—On March 1, 1953, in a nursing-home, Edinburgh, William Fraser MacDonald, M.B., Ch.B., of Olive Lodge, 42, Polwarth Terrace, Edinburgh.
Mason.—On February 28, 1953, Maurice Charles Mason, M.R.C.S., L.R.C.P., D.O.M.S., Surgeon Commander, R.N., retired, of Quarry Cottage, St. Leonards-on-Sea, Sussex, aged 67.
Moorhead.—On March 1, 1953, at Chipping Campden, Glos, the result of an accident, Charles Edward Moorhead, O.B.E., M.B., Ch.B.
Popham.—On March 1, 1953, at The Croft, Wrekenton, Co. Durham, Henry Nicholas Popham, M.B., B.S.
Russell.—On March 5, 1953, at Northcote House, Blackwater, Camberley, Surrey, Walter Ralph Russell, M.R.C.S., L.R.C.P., D.Obst.R.C.O.G., D.C.H.
Sawyer.—On February 22, 1953, James Edward Hill Sawyer, M.D., M.R.C.P., Lieutenant-Colonel, R.A.M.C., T.A.R.O., retired, of Little Holton, Burwash, Sussex, aged 78.
Skrimshire.—On March 2, 1953, at Hill House, Holt, Norfolk, Henry Finch Skrimshire, M.R.C.S., L.R.C.P., aged 79.
Star.—On February 19, 1953, Paul Hohling Mills Star, O.B.E., M.R.C.S., L.R.C.P., Surgeon Captain, R.N., retired, of Long Ashton, Somerset, aged 82.
Trimmer.—On February 27, 1953, at Orpington Hospital, Kent, Francis Inman Trimmer, M.R.C.S., L.R.C.P., late of 22, Sherard Road, Eltham, London, S.E.
Willox.—On February 25, 1953, in a Glasgow nursing-home, Leonard Stephen Willox, M.D., D.P.H., of Leabank, Dumbarton.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

Wassermann Test in Infancy

Q.—*What is the earliest age at which the result of a Wassermann test on a newly born infant can be regarded as conclusive? This is a problem when babies are offered for adoption.*

A.—It is assumed from the question that the child's mother has suffered from syphilis. If this is the case, the result of one blood test would not be conclusive evidence. If a Wassermann reaction done within a week of birth is negative, it is almost certain to remain so when tested later. Nevertheless, a second test should *invariably* be carried out when the child is 3 months old.

If the first test is positive it may be due to : (1) A "carry over" of reagin from the mother, in which case the child's Wassermann titre will usually be lower than its mother's. On serial quantitative testing the positive serum titre of the child will show a progressive and uninterrupted fall, until it finally becomes negative at about 1 to 3 months, depending on the amount of reagin present at the time of the first test and the sensitivity of the serum tests employed. (2) Infection : in this case the Wassermann titre of the child's serum will remain stationary or rise during the course of a series of fortnightly quantitative blood tests.

Specimens of cord blood should never be sent to a laboratory for testing, because a positive result may be of no significance owing to the presence of its mother's reagin ; also, many such specimens have an anticomplementary action due in most cases to infection, but in some to an inherent property of this type of serum.

Iodine for Water Sterilization in the Field

Q.—*I understand that American forces in Korea have been using iodoglobulin for water sterilization. Please describe the method and compare its advantages and disadvantages with chlorination.*

A.—The American specification (Mil.-T.-283A, dated December 7, 1950) for "Tablets, Water Purification, Individual, Iodine" requires each tablet to weigh not more than 120 mg. The tablets are to contain tetraglycine hydroperiodide 19.3 to 21.3 mg., sodium acid pyrophosphate 82.5 to 92.3 mg., and inert materials to be not more than 5% by weight. Each tablet must contain between 7.6 and 9.0 mg. of titratable iodine. The instructions for use require the addition of one tablet to a quart (about a litre) of water, and a wait of 10 minutes, or 20 minutes if very cold, before drinking. Two tablets are used instead of one if the water is dirty and discoloured. The tablets are packed in bottles of six, twenty-five, or fifty. So far as we are aware no other iodine preparations are being supplied to the American Army.

The advantages of iodine compared with chlorine are : (*a*) it does not form with ammonia slow-acting (on organisms) ammonia compounds—for example, chloramine ; (*b*) it is not affected in its sterilizing properties by the reaction (*p*H value) of the water ; (*c*) it is not so easily deviated by organic and other constituents of the water as is chlorine ; and (*d*) it is reported to be more lethal to cysts of *Entamoeba histolytica* than chlorine.

Neither chlorine nor iodine has any bad physiological action when consumed in small quantities. Recent human feeding tests by the Americans have shown that a human being can tolerate 70 mg. of iodine daily without untoward effects. Iodine has the disadvantages that it is expensive and it colours the water yellow. This is regarded as an advantage by some people, as it shows that the water has been treated with iodine and is presumably safe to drink.

Exercises in Bed after Operation

Q.—*What routine bed-exercises are recommended to forestall thrombotic and pulmonary complications in patients after abdominal and thoracic operations, from the operation to the fourteenth day?*

A.—Post-operative bed-exercises can be divided into three main groups—breathing, leg, and abdominal. These are sometimes supplemented by arm and back exercises, but the latter will not be described here.

The details of treatment must obviously be varied according to the general condition and age of the patient. With a really ill patient the usual routine is : breathing ; ankle, foot, and quadriceps exercise ; further breathing ; gentle hip and knee exercises ; final breathing, with percussion if needed. For a recovering patient this routine is made gradually more vigorous up to the convalescent stage. The three main groups of exercises are carried out as follows :

Breathing.—The physiotherapist gives three types of breathing exercise—abdominal, lower thoracic, and upper thoracic. The first two increase diaphragmatic movement, and by giving the exercise against manual resistance the physiotherapist encourages the patient to "feel" the type of movement required. Breathing must be done slowly and deeply about six times and followed by a rest. The patient should concentrate upon the fullest possible inspiration and expiration. This is of real value in assisting the venous return as well as in preventing pulmonary collapse. Coughing should be encouraged, especially if there is any sputum, early rise of temperature, or other signs of pulmonary collapse. Springing the chest smartly (with hands on the ribs at each side, or with one hand over the sternum), especially during expiration, assists in expulsion of the bronchial secretions. It is best for the patient to sit up, leaning slightly forward and supporting the abdominal wound with his own hands. An alternative to springing the chest is clapping over the back with *cupped and relaxed hands*. Slapping the back can be painful and may cause the patient to tense his muscles. The great secret of all these coughing and springing exercises is to work away at them gradually until the patient attains confidence. There is little difference in the management of cases with abdominal or thoracic wounds, although special posturing and intensified physiotherapy may be needed in certain chest cases, such as following pulmonary resection for bronchiectasis.

Leg Exercises.—In the ill patient these are limited to bending and stretching of toes, pedalling the feet up and down, and ankle-rolling exercises. This may be followed by simple quadriceps drill : alternate lifting of the legs off the bed with knees straight, and sliding the heels up to the buttocks and down again. In the recovering patient these exercises are increased in range and vigour to include leg raising and circling, elevation and abduction of the straight leg, and sitting over the edge of the bed with legs swinging.

Abdominal Exercises.—Gentle exercises are done with the patient supine and the knees crooked up : the head and shoulders are then gently raised and lowered. More vigorous exercise of the oblique muscles is given by trunk-turning with arms stretched out sideways, and the patient then alternately touches each side of the bed with his hands. These can be supplemented by lateral bending of the trunk and back arching in the supine position.

The questioner has asked for information about bed-exercises from the operation to the fourteenth day, but it should be emphasized that it is of the utmost importance to train the patient *before* the operation. The amount of training required will vary both with the individual patient and with the operation. Full instruction in breathing exercises, and especially the diaphragmatic ones, is extremely important for male patients.

No answer would be complete without reference to the value of early ambulation as a supplement to these bed-exercises. The patient must, however, be up and *active*. It is certainly better for an ill patient to remain warm and gently exercising in bed than to be got up and allowed to slump in an armchair with bent and inactive legs. Although there is some difference of opinion about the value of early ambulation in preventing thrombo-embolic complications, there can be no doubt about its general moral and physical value to the patient. It is doubtful whether fatal embolism is much reduced, but troublesome leg thromboses are probably less frequent. In general, rising should begin between the second and fourth post-operative days ; there is no

real virtue in immediate ambulation after operation. The subject of early ambulation was fully discussed in a leading article (*British Medical Journal*, 1948, **2**, 1026).

Mixtures of Antibiotics

Q.—*What mixtures of antibiotics can be given at the same time? Are any pharmacologically incompatible, and do the antibacterial actions of some neutralize those of others?*

A.—There is no incompatibility between antibiotics in a pharmaceutical sense, but if by "pharmacologically" is meant an interference by one with the action of another this undoubtedly can occur. Such effects can readily be demonstrated *in vitro* and in some conditions experimentally *in vivo* when an antibiotic the action of which is mainly bacteriostatic or growth-inhibitory (aureomycin, chloramphenicol, or terramycin) is added to one which is bactericidal or directly lethal to bacteria (penicillin or streptomycin). Antibiotics of the latter class act only on multiplying bacteria, and if multiplication is prevented by the presence of a bacteriostatic substance their lethal effect is naturally delayed. This interference is closely conditioned by antibiotic concentration, bacterial sensitivity, and dose–time relationships, and it is uncertain how often it operates in the clinical field. A clear example of interference seems to be afforded by the experience of Lepper and Dowling,[1] who treated 43 patients with pneumococcal meningitis with large doses of penicillin only, of whom only 13 died (30%); of 14 patients also given aureomycin, 11 died (79%).

REFERENCE

[1] *Arch. intern. Med.*, 1951, **88**, 489.

Cats at Night

Q.—*How do cats see in the dark?*

A.—No animal, not even a cat, can see in the dark, because if visual rays are completely absent the retinae cannot receive adequate stimulation. At the same time it must be admitted that many animals may be able to see under conditions which would not permit a human observer to do so. A number of different factors may act in combination in producing this difference. Of all the light which falls on the front of the eye from external objects probably little more than one-tenth finds its way in through the human iris even when this is widely dilated. This is because the F value (the ratio of focal length to aperture) in man seldom exceeds two. In cats, on the contrary, it may equal one, and, since the brightness of the image on the retina is inversely proportional to the square of the F value, it follows that in a cat this may be four times as bright as in a man. Having passed in at the pupil, a certain proportion of the light is absorbed by the crystalline lens and by the vitreous humour. In those animals which have small eyes with short paths through crystalline and vitreous these losses are less than they are in a human eye. Thus in this respect a cat is better off than a man and a mouse better off than either. It is possible that rays at the extreme ends of the spectrum, that is in the red and in the violet, may be made use of by small animals for visual purposes, whereas to a man they are practically useless because of their low intensity. In this connexion it may be of interest to recall the fact that patients who have had to suffer the loss of a crystalline lens are compensated to some extent by being able to see by means of violet and even by ultra-violet rays, which they were never able to do while the eye was intact. Having reached the human retina, most of the light is absorbed, in part by the photosensitive pigments, such as visual purple, on which sight depends, and in part by the pigment in the outermost layer of the retina. In many animals this layer constitutes a reflecting screen, or tapetum, by means of which the light is returned through the retina a second time. It is thought that this increases sensitivity to light at the expense of fine definition. Theoretically there are two other ways in which the retina could be made more sensitive still, by concentration of the photosensitive pigments, and by linking more receptor cells to each of the optic nerve fibres. Now, suppose that all these modifications are to be found in the eyes of a particular category of animal, to what extent should we expect its eyes to show an improvement in performance? Only a very rough guess is possible—namely, that the animal in question may require no more than one-tenth of light than is required by a man for the same visual performance under twilight conditions. It should be emphasized that this advantage is not obtained without the introduction of disabilities. Usually it is visual acuity which is sacrificed. Thus the employment of a larger F value means that the more peripheral zones of the lens-system are brought into use, and these have more marked aberrations than the central zones, thus reducing visual acuity. The situation may perhaps be summed up as follows: In the design of the human eye resolving power has been given prior consideration, but in the design of other eyes other factors appear to have been more important. In the case of cats this seems to have been the ability to see in very poor light.

Efficacy of Abortifacient Drugs

Q.—*How effective are the drugs commonly used in criminal attempts to secure abortion, in particular extract of ergot?*

A.—Drugs such as strong aperients, lead, quinine, oxytocin and ergot preparations are almost completely ineffective as abortifacients in normal women, although they might disturb a pregnancy in a woman who has an unusual susceptibility to abortion. The ineffectiveness of such preparations *by themselves* is well illustrated by the fact that they are now rarely, if ever, even tried when therapeutic abortion is indicated. Moreover, it was not uncommon in the past to see pregnancy continue unaffected in women who had taken so much in the way of drugs that they themselves suffered from lead, quinine, or ergot poisoning. Again, quinine is given with impunity in malaria-infested countries, and ergot preparations can be safely used for migraine up to the last few weeks of pregnancy.

The oxytocics mentioned become more effective if they are used as supplements to local interference in the uterus—for example, rupture of the membranes, dilatation of the cervix, or intrauterine injections.

Safety of the Safe Period

Q.—*What are the chances of conception occurring as a result of intercourse during the "safe period" in a young married woman with a regular menstrual cycle?*

A.—In such circumstances conception is very unlikely, but it is always possible. The chances cannot be stated statistically, and they may well vary according to the exact day in the "safe period" on which coitus takes place.

NOTES AND COMMENTS

Corrections.—Dr. J. R. HINDMARSH writes to say that in the article by him and Dr. D. Emslie-Smith (March 14, p. 593) the second paragraph should read: "Uncomplicated leukaemia presenting as acute polyarthritis has been described by many authors, and its rarity *outside* childhood . . ." not "in childhood."

The *Textbook of Medical Treatment* edited by Dunlop, Davidson, and McNee referred to in our review columns in the issue of March 21 (p. 661) was incorrectly entitled *Textbook of Medical Practice*.

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